## Commercialisation of a novel microRNA replacement therapy for equine and human tendinopathies

**1. Summary of the impact**

Tendinopathies are a debilitating category of sports injury, affecting 10% of people and 15%–30% of working and performance horses. UofG researchers identified a first-in-class regenerative therapy ( **miRNA29a**) that restores injured tendons to normal structure and function. In 2015, **Causeway Therapeutics Ltd (CTL)** was created as a UofG spin-out to commercialise *miRNA29a*. CTL has attracted approximately GBP13.0 million in investment to advance veterinary ( **EquiMiR™**) and human ( **TenoMiR™**) versions of *miRNA29a*, indications that currently lack a market competitor. In August 2019, EquiMiR™ entered an experimental dose-finding and efficacy trial (36 horses), with regulatory approval secured for a multicentre pivotal veterinary trial. A 6-month first-in-human phase 1b clinical trial of TenoMiR™ among 24 patients with tennis elbow commenced in September 2020.

### 4. Details of the impact

**A novel approach to tendinopathy: microRNA replacement therapy**

The standard treatment for tendinopathy is physiotherapy for people and 6–9 months’ box rest for horses. Nonsteroidal anti-inflammatory drugs can be used but these agents are only palliative and do not target the underlying disease mechanism. Furthermore, the widespread uptake of biological therapies, such as platelet-rich plasma and autologous stem-cell injections, is limited by their ineffectiveness, restricted scalability and lack of understanding about their mode of action.

Replacement therapy with miRNA29a overcomes these hurdles. First, unlike other therapies, it directly targets the disease pathway and restores damaged tendon. Second, it can be chemically synthesised through an automated process and has a predicted shelf life of at least 2 years, thereby reducing manufacturing costs. Third, it can be delivered directly to the target tendon using ultrasonographic-guided injection, decreasing both systemic exposure and the dosage required for treatment.

UofG research on biological mechanisms underlying tendinopathy [3.1–3.3] and the proof-of-concept study of miRNA29a as a novel therapy [3.4] established **commercial pathways** for both equine and human indications. These pathways have progressed through:

**(1)** creation of a UofG spin-out company (CTL);

**(2)** securing funds from investors;

**(3)** obtaining patents for the miRNA29a replacement technology;

**(4)** forming a co-delivery partnership for development of EquiMiR™;

**(5)** securing UK, EU and US ethical and regulatory approvals for equine and human trials; and

**(6)** commencing trials for both EquiMiR™ (USA) and TenoMiR™ (UK).

**CTL established to commercialise miRNA29a**

CTL was co-founded by **Millar** and **Gilchrist** in 2015, with **McInnes** as the Lead Medical Advisor, to commercialise the miRNA29a replacement therapy for both equine and human indications [5.A].

During 2017–2020, CTL has attracted approximately GBP13 million in investment [5.B], with a current company valuation of GBP15 million. Initial seed investment of GBP1 million from  **[Mediqventures](https://www.mediqventures.com/)** and the  [**Scottish Investment Bank**](https://www.scottish-enterprise.com/our-organisation/about-us/who-we-work-with/scottish-investment-bank) provided a development runway to 2020 [5.B], enabling CTL to employ four full-time staff and develop EquiMiR™ and TenoMiR™ as its lead products. On announcing this funding, the Head of the Scottish Investment Bank stated: “ Scottish Enterprise, through the Scottish Investment Bank, is delighted to be co-investing with Mediqventures to help the company fully commercialise its technology. We have supported Causeway Therapeutics through our High Growth Ventures Programme to help with company formation, research and now investment to help it grow to the next stage. We look forward to working alongside Causeway to help it achieve its potential, both in Scotland and internationally” [5.B]. In 2020, CTL announced that a new round of venture capital investment opportunity would commence during January–March 2021 to raise GBP15 million in funding for the next phase of the company’s development [5.B].

CTL holds the intellectual property for miRNA29a replacement therapy, with **Millar** and **Gilchrist** named as the inventors on patents describing this technology as a novel method to improve tendon healing [5.C]. Patents have been granted in Europe (December 2017), the USA (April 2018), Canada (August 2018), Hong Kong (September 2018) and Russia (July 2019) [5.C]. Applications are pending in Australia, New Zealand, Saudi Arabia, United Arab Emirates, Japan and China.

**Veterinary trials of EquiMiR™ as a treatment for tendinopathy**

The equine indication for miRNA29a has a potential market of GBP120 million in the UK and over USD600 million in Europe and the USA [5.A]. EquiMiR™ is expected to dominate the treatment of equine lameness as no other pharmacotherapies currently exist within this disease area and none has been developed since the collagen-crosslinking inhibitor Bapten, which was removed from the market in 1998. Therefore, commercialisation of the UofG miRNA29a replacement therapy will benefit equine health and welfare, particularly in racing, as horses treated with EquiMiR™ are less prone to reinjury than are horses managed conventionally. Racehorses receiving EquiMiR™ are also less likely to be culled following premature termination of their competitive careers, providing substantial value to owners and trainers. Finally, use of EquiMiR™ would avoid lengthy periods of box rest for injured animals, thereby limiting lost days of training and racing.

In September 2014, EquiMiR™ received Minor-Use-Minor-Species recognition from the European Medicines Agency, which appreciably reduces the amount of data required to obtain a Marketing Authorisation from this regulatory body [5.D]. EquiMiR™ also received a fee waiver from the US Food and Drug Administration (FDA) under the Barrier-to-Innovation provision of the Animal Drug User Fee Act (July 2016) [5.E]. This waiver accelerates the development and regulatory process of EquiMiR™ towards marketing authorisation in the USA. These two regulatory approvals considerably decrease the cost of drug development and production, which will ultimately reduce the final price for end users of EquiMiR™.

Through the UofG research collaboration with Texas A&M University [3.4], CTL was introduced to [redacted], a mid-sized UK-based international veterinary pharmaceutical manufacturer with appreciable access to the equine market. In August 2017, CTL signed [redacted] as a co-delivery partner to share EquiMiR™ product development and be responsible for retail and distribution. [Redacted] has contributed GBP8 million to development costs to support safety studies, equine trials and regulatory approval, which includes GBP3 million in milestone payments to CTL. This partnership provides [redacted] with access to CTL’s cutting-edge research and development capability, and so will position it as the field leader in treating equine lameness.

In 2019, EquiMiR™ underwent a 6-month experimental dose-finding and efficacy trial at Texas A&M University using the equine collagenase-induced tendonitis model. Substantial improvements in structural parameters were demonstrated by ultrasonography among 36 horses treated with high doses of EquiMiR™ (findings not yet publicly available). An FDA-approved pivotal veterinary trial is scheduled to commence at several US sites in 2021 (originally due to start in 2020 but stalled owing to COVID-19).

**Clinical trials of TenoMiR™ as a treatment for tendinopathy**

The market for treating tendinopathy in humans is valued at USD5 billion worldwide [5.A]. Potential indications for TenoMiR™ include lateral epicondylitis (tennis elbow), which is predicted to be worth USD903 million in the USA, EU and Japan by 2020 [5.A]. As a first-in-class therapy, there is currently no competitor for TenoMiR™ in this clinical arena.

Recognising the success of CTL in developing EquiMiR™ [3.4], Mediqventures and the Scottish Investment Bank invested an additional GBP1 million in 2018 [5.B]. This funding—together with grants from Innovate UK of GBP1.4 million (2018) and GBP1.3 million (2019) [5.B]—accelerated the development of TenoMiR™ for human indications, particularly the preclinical packages required for filing an Investigational New Drug application. In 2020, CTL received a GBP230,986 Innovate UK COVID-19 Continuity Grant that enabled clinical work on TenoMiR™ to proceed during the pandemic [5.B].

Data from the equine studies of the miRNA29a replacement therapy supported regulatory filings by CTL to conduct first-in-human clinical trials of this approach. An NHS Research Ethics application was approved in September 2019, with TenoMiR™ designated as an Investigational New Drug by the UK Medicines and Healthcare Products Regulatory Agency in August 2020 [5.F]. In September 2020, a phase 1b clinical trial of TenoMiR™ commenced in Manchester among 24 patients with tennis elbow (8 patients enrolled as of November 2020) [5.F]. With a positive read-out from this trial expected to occur before May 2021, CTL will actively seek larger pharmaceutical partners either to sell or co-develop TenoMiR™. In addition, CTL has extended its preclinical development pipeline to other novel miRNA replacement therapies targeting conditions such as osteoarthritis and intravertebral disc disease (OsteoMiR™); skin ageing (DermaMiR™); and wound healing ( miRNA-148b) [5.F].