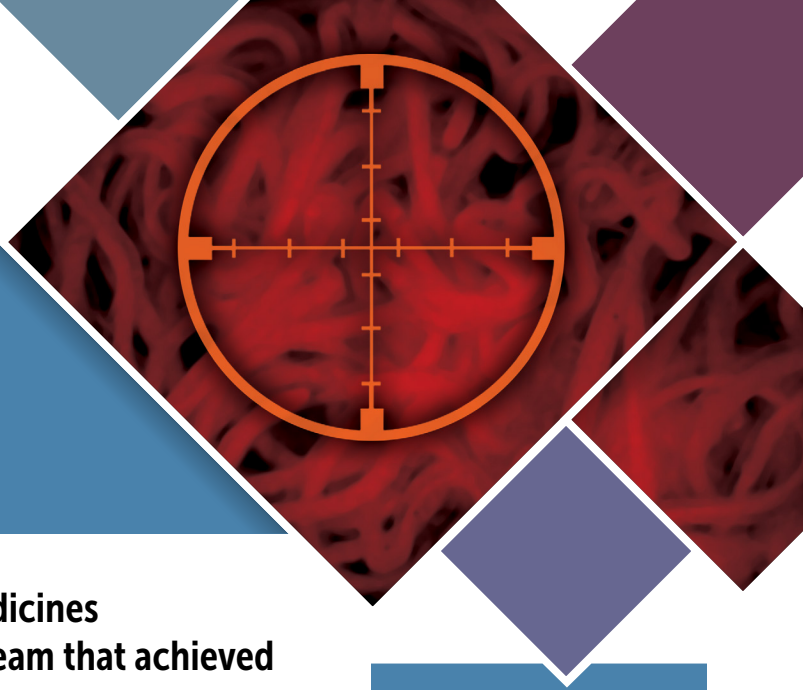
CERTARA

Supporting the Approval of a Treatment for a Neglected Tropical Disease



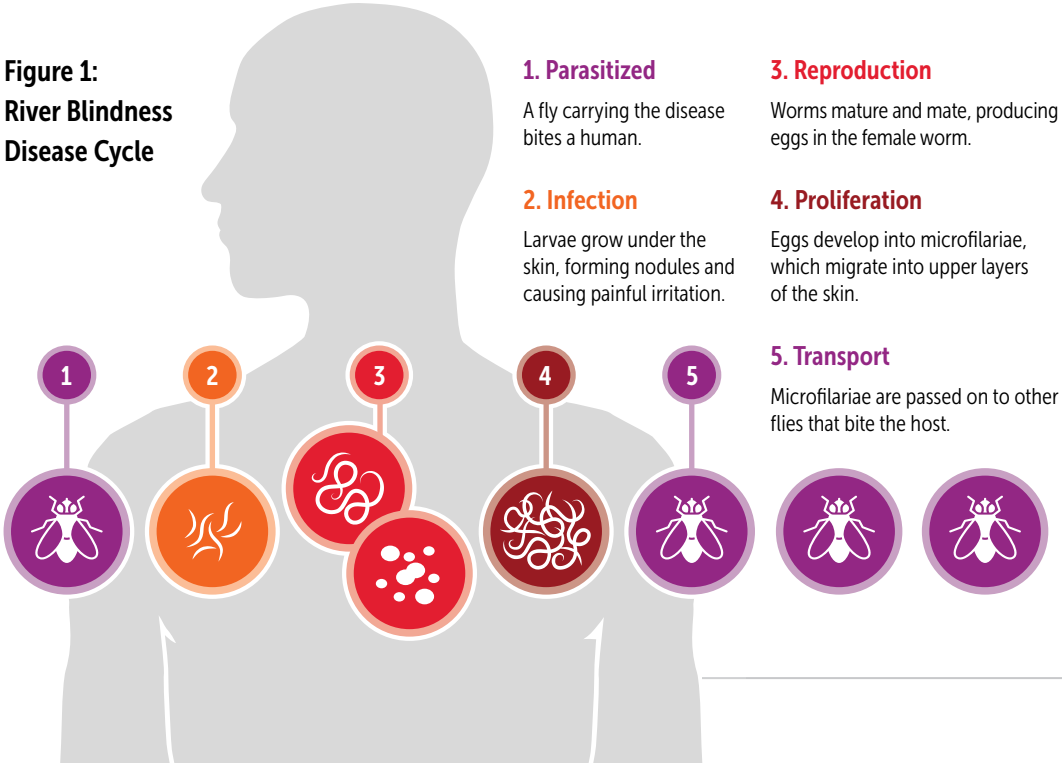
Certara scientists were key members of the Medicines Development for Global Health development team that achieved FDA approval of moxidectin for river blindness.

Background

Medicines Development for Global Health (MDGH) is a not-for-profit biopharmaceutical company headquartered in Melbourne, Australia. MDGH is dedicated to developing affordable medicines and vaccines for neglected diseases prevalent in low- and middle-income countries.

Onchocerciasis (river blindness) is a Neglected Tropical Disease (NTD). It is the second leading cause of infectious blindness and the fourth leading cause of preventable blindness worldwide. Onchocerciasis is endemic in some of the world's poorest and most disadvantaged communities, affecting at least 25 million people worldwide. It is caused by the nematode, *Onchocerca volvulus*, which is transmitted by *Simulium* black flies that breed in fast-flowing rivers (Figure 1). The millions of larvae (microfilairae) released by the adult parasites invade patients' skin, lymph nodes and eyes. The worms can cause skin inflammation, intense itching, enlarged lymph nodes, and, in some patients, visual impairment that can lead to blindness.

Figure 1: River Blindness Disease Cycle



1. Parasitized

A fly carrying the disease bites a human.

2. Infection

Larvae grow under the skin, forming nodules and causing painful irritation.

3. Reproduction

Worms mature and mate, producing eggs in the female worm.

4. Proliferation

Eggs develop into microfilariae, which migrate into upper layers of the skin.

5. Transport

Microfilariae are passed on to other flies that bite the host.

Challenge

MDGH needed integrated, model-informed drug development expertise to support the development of moxidectin as an oral treatment for onchocerciasis.

Solution

Certara provided expertise to MDGH, including membership on the development governance committee, leadership of clinical pharmacology and pharmacometrics, and support for translational medicine, regulatory science, and strategy activities.

Benefit

Certara's approach yielded a significant financial, scientific, and regulatory ROI to MDGH, culminating in FDA approval and receipt of a tropical disease priority review voucher.

Challenge

In sub-Saharan Africa, where onchocerciasis is endemic, the standard of care is administered once (annual community-directed treatment with ivermectin: aCDTI) or twice a year (biannual CDTI: bCDTI) as part of mass drug administration (MDA) programs. Unfortunately, epidemiological modeling has shown that aCDTI is unlikely to achieve the 2012 London Declaration on Neglected Tropical Diseases goal of eliminating onchocerciasis in 80% of endemic countries by 2025. Thus, alternative treatments were needed.

Moxidectin is a macrocyclic lactone anthelmintic drug. It was first developed as a veterinary product and is registered worldwide for the prevention of canine heartworm and for the treatment of livestock parasites. Moxidectin has several features that make it suitable as a global health medicine. It can be administered orally, has extensive tissue distribution, and has a long half-life of 20 to 40 days, which facilitates infrequent dosing. However, this drug was not registered for human use.

MDGH secured the rights to develop moxidectin for human use from the World Health Organization (WHO) Special Program for Research and Training in Tropical Diseases (TDR) in 2015. This client needed integrated, model-informed drug development expertise in the areas of clinical pharmacology, translational medicine, and regulatory science to support the development of moxidectin as an oral treatment for onchocerciasis.

Solution

Certara scientists provided a variety of expertise to MDGH's global virtual development team for moxidectin for river blindness. This included membership on the development governance committee, leadership of clinical pharmacology and pharmacometrics (modeling and simulation), and support for MDGH's translational medicine, regulatory science, and strategy activities.

Pharmacokinetic/pharmacodynamic modeling and simulation (PK/PD M&S) was applied throughout the program to expand the development team's knowledge of moxidectin. Specifically, the Certara team used population PK/PD models to support the therapeutic dose rationale and to understand the potential impact of intrinsic (eg, body composition, gender, age, disease burden) and extrinsic (eg, concomitant medications, food, formulation) factors on moxidectin dosing and use.

This model revealed that increased systemic drug exposure corresponded to an increased probability of sustained microfilarial response (SMR) in the skin and decreased ocular burden over 12 months.

Modeling and simulation methods also informed clinical trial design, conduct, and analyses. Those trials included a concentration QT (cQT) study to assess the potential for cardiotoxicity and selection of doses for a pediatric Phase 2 study.

MDGH and Certara also collaborated with teams from TDR and Imperial College London to combine PK/PD modeling with epidemiological and health economic outcomes research (HEOR) modeling to explore public health strategies that could accelerate eliminating onchocerciasis.

Lastly, Certara provided regulatory support to the moxidectin program. Certara scientists authored key new drug application (NDA) documents and supported all major face-to-face meetings with the FDA.

Benefit

The integrated and creative approach that Certara used for moxidectin yielded a significant financial, scientific, and regulatory ROI to this client. As a co-investigator with MDGH, Certara helped attract approximately $8 million in grants for clinical trials and epidemiology/HEOR modeling.

By combining the absorption, distribution, metabolism, and excretion (ADME) and cQT studies, MDGH was able to complete these studies with only 50 subjects. Traditionally, these studies would require multiple studies with hundreds of subjects.

The use of M&S was also critical in driving greater efficiency. Modeling approaches were leveraged to bridge the new market formulation to historic data, despite not having information on retained clinical formulations used. M&S was also employed to "retrofit" the dose rationale for the moxidectin program. This enabled the use of only a single Phase 3 clinical trial and exposure-response data from a Phase 2 study to support an approval.

Determining the retreatment interval for dosing with moxidectin had to be addressed to make it a successful public health intervention. Moxidectin was only evaluated in clinical trials at a single dose. Yet, application in the field would require multiple dosing. The Certara team expanded their pharmacological and epidemiological modeling methods to justify the moxidectin retreatment interval. Using epidemiological modeling to justify the dosing interval in a regulatory filing is unprecedented.

This modeling demonstrated that—for a given patient population, treatment frequency, and coverage—moxidectin could significantly shorten the time to eliminate onchocerciasis compared to current ivermectin strategies (Table 1). The increased cost incurred with biannual moxidectin distribution (bCDTM) indicates that annual moxidectin (aCDTM) would be more economically viable than the currently proposed alternative treatment strategy of switching from aCDTI to bCDTI. To achieve the fastest possible eradication or for areas of very high pre-treatment endemicity, bCDTM could be used and remains more economical than bCDTI.

Table 1: Years to Elimination (% Reduction Relative to aCDTI)

MDA Scenario	aCDTI	bCDTI	aCDTM	bCDTM
Mesendemic Focus (community microfilariae load = 9.1 mf/skin snip, prevalence < 60%)				
Standard	22	19 (14%)	19 (14%)	17 (23%)
Enhanced	18	14 (22%)	14 (22%)	11 (39%)
Hyperendemic Focus (community microfilariae load = 31.3 mf/skin snip, prevalence > 70%)				
Standard	30	26 (13%)	26 (13%)	23 (23%)
Enhanced	17	15 (12%)	15 (12%)	13 (24%)

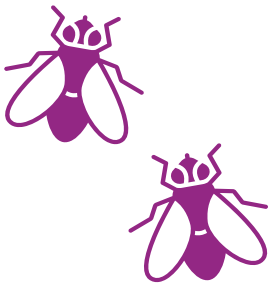
* Standard MDA: 65% therapeutic coverage, 5% systemic non-compliance
** Enhanced MDA: 80% therapeutic coverage, 1% systemic non-compliance

Thus, moxidectin has the potential to deliver enormous public health benefits. In collaboration with the WHO, Imperial College, and the World Bank, these insights were leveraged to support an investment thesis for bCDTM.

Impact

The FDA approved MDGH's NDA for moxidectin on June 13, 2018 and granted them a tropical disease priority review voucher. MDGH is the first not-for-profit biopharmaceutical company to achieve FDA approval as the sole sponsor, and also, the first not-for-profit awarded a priority review voucher from the FDA. This voucher—an incentive to spur development of medicines to treat neglected diseases—is a tradeable instrument that can be applied to accelerate review of any sponsor's drug. The priority review voucher has a current market value between $100–200 million.

MDGH is committed to continuing moxidectin development for other indications including scabies, lymphatic filariasis, soil-transmitted helminths, and strongyloides, which are all neglected tropical diseases affecting up to one billion people. Certara will continue to partner with MDGH to achieve these goals.



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About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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