2021

Medicines Development
for Global Health

2021

Annual Report

Letter from the Board Chair

Lorna Meldrum

The often misquoted expression “May you live in interesting times” is not, in fact, a blessing, but rather a curse. It seems quite the appropriate quote to explain the challenges the world has been facing these past two years as we try to pull ourselves out the sea of doubt, confusion, misinformation, and the uncertainties for our future. Yet, as challenging as these times have been, we’ve seen, repeatedly, the resiliency of the human spirit.

The Covid-19 pandemic has taken its devastating toll on the world, with little to no regard for gender, religion, ethnicity, or economics. More fortunate countries and communities were able to carry on with their lives and livelihoods, albeit in the form of a virtual world, whether through online classes or online business meetings. But for many of those living in low- and middle-income countries, where internet connectivity is not something taken for granted, where the routine public gatherings for school and market days were cancelled, work and life came to a crashing halt as the pandemic burned in full force.

The most dire effects of the pandemic were seen in disruptions to community-directed treatment programs in many of the poorest and most affected communities.

The impact of the pandemic was felt particularly hard within the global public health community. Funding and resources originally allocated to neglected tropical disease programs were diverted to Covid-related efforts. Ongoing clinical trials were shut down during periods of highest Covid outbreaks.

The lack of resources in the supply chains needed to support implementing the scheduled distribution and delivery of vital medicines resulted in interruptions of these programs, with upwards of 75% of treatments delayed. Fortunately, no community-directed treatment programs were cancelled or delayed to the point of severe detriment.

The pandemic caused the world to slow its social and economic engines. But the neglected infectious diseases of the world continued to rage on. These diseases and their vectors remained virulent. While the pandemic disrupted the normal flow of goods and services throughout the world and, in particular, the global public health community, tireless efforts from those invested in helping to eliminate many of the world’s most devastating diseases have continued unabated. You do not always see the product of their efforts, but, behind the scenes, countless forces have been working to find solutions to circumvent the crippling effects of this pandemic.

Hopefully, we have seen the worst of this deadly disease as we slowly emerge from the wake of its devastation. It is only now that many community-directed treatment programs are emerging from the Covid crisis and re-engaging in their implementation efforts.

At Medicines Development for Global Health, we have lived through the most trying of times during this pandemic. In our headquarters in Melbourne, our staff have faced multiple periods of lockdown. Slowdowns in patient recruitment for vital clinical trials and delays in program implementation have pushed back some of our anticipated end dates. But that has not stopped dedicated staff from continuing the advances we have made during this past challenging year. As a small but nimble organisation we have figured out how to carry on – how to progress.

We invite you to learn more about what Medicines Development for Global Health has been doing during these challenging times in our continuing efforts to bring necessary medicines to those most in need.

Lorna Meldrum, PhD

Chair of the Board,
Medicines Development for Global Health

Letter from the Managing Director

Mark Sullivan

In the foreword to Bruce Benton's history of the collaboration of international development partners in the fight against onchocerciasis in his book River Blindness in Africa: Taming the Lion's Stare, Sir James Wolfensohn, former president of the World Bank, highlights the years lost "…that otherwise would be a prime time for providing for one's livelihood, supporting a family, and contributing to the community". While he is talking about the devastating effects of river blindness, Sir James' comments could easily be ascribed to any number of neglected tropical diseases.

At Medicines Development for Global Health, we are working on accelerating elimination with moxidectin for river blindness, but our ambition does not end there: we have a broad portfolio of activities in lymphatic filariasis, scabies, soil-transmitted helminths, and strongyloidiasis. For CC-11050, our work continues to address leprosy type 2 reaction and tuberculosis. All told, these are among the neglected diseases that affect over 1.7 billion people globally: that's one out of every five people on the planet.

That the Covid-19 pandemic has taken a significant toll on life, livelihoods, health, and mental health around the world is not news. At Medicines Development for Global Health, the pandemic has impacted work near and far: the shift to remote working was bitter/sweet but the delays to our clinical trials are shared by everyone conducting non-Covid-related studies. Our paediatric clinical trial in Ghana, the river blindness trials in the Democratic Republic of the Congo, the scabies trials in Europe and Australia, and our collaborative studies in South Africa on tuberculosis and Nepal on leprosy type 2 reaction have all been delayed.

Yet, at the same time, we have managed to make good progress in many areas. Encouraging preliminary data from the first clinical trial assessing moxidectin as a potential treatment option for lymphatic filariasis was presented late last year at the American Society of Tropical Medicine and Hygiene conference in a study sponsored and conducted by the Washington University (St. Louis, USA) Death to Onchocerciasis and Lymphatic Filariasis (DOLF) Project. The data have triggered significant interest in advancing clinical trial development efforts and Medicines Development for Global Health is in discussion with the DOLF team, the World Health Organization and the Bill & Melinda Gates Foundation, about the next phase of clinical trials to add moxidectin to the existing treatment armamentarium for lymphatic filariasis.

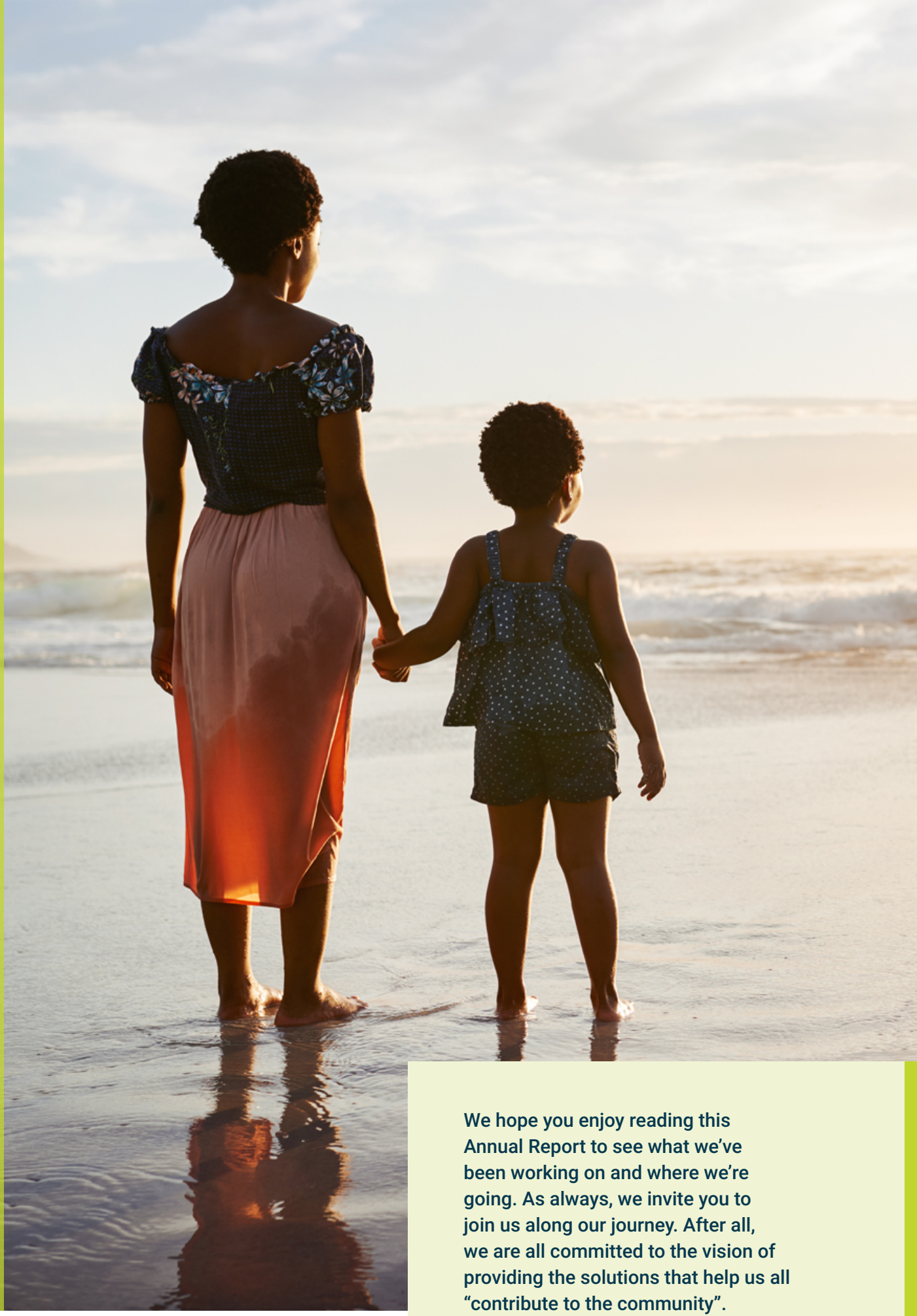
Neglected tropical disease medicines have a pivotal "second hurdle" to cross once a stringent regulatory authority approval has been achieved: the World Health Organization endorsement. While Medicines Development for Global Health continues to generate the clinical trial data required for the World Health Organization review, the World Health Organization Onchocerciasis Technical Advisory Subgroup has endorsed the use of moxidectin in pilot treatment programs. This favourable recommendation paves the way for countries to develop local implementation strategies using moxidectin as a treatment option.

As we continue to move forward with development efforts for moxidectin and CC-11050, we are mindful of the urgency in bringing new medicines, new solutions, to the challenges presented by the various neglected tropical diseases. It is a commitment we do not undertake lightly. And it is a commitment we make as a member of a much larger global public health community.

Medicines Development for Global Health remains a small but agile, not-for-profit organisation working across a broad array of collaborators and external resources to deliver on our pledge to help eliminate Neglected Tropical Diseases. We thank all our partners – collaborators and funders alike – who continue to support our development goals.

Mark Sullivan, AO

Managing Director,
Medicines Development for Global Health



We hope you enjoy reading this Annual Report to see what we've been working on and where we're going. As always, we invite you to join us along our journey. After all, we are all committed to the vision of providing the solutions that help us all "contribute to the community".

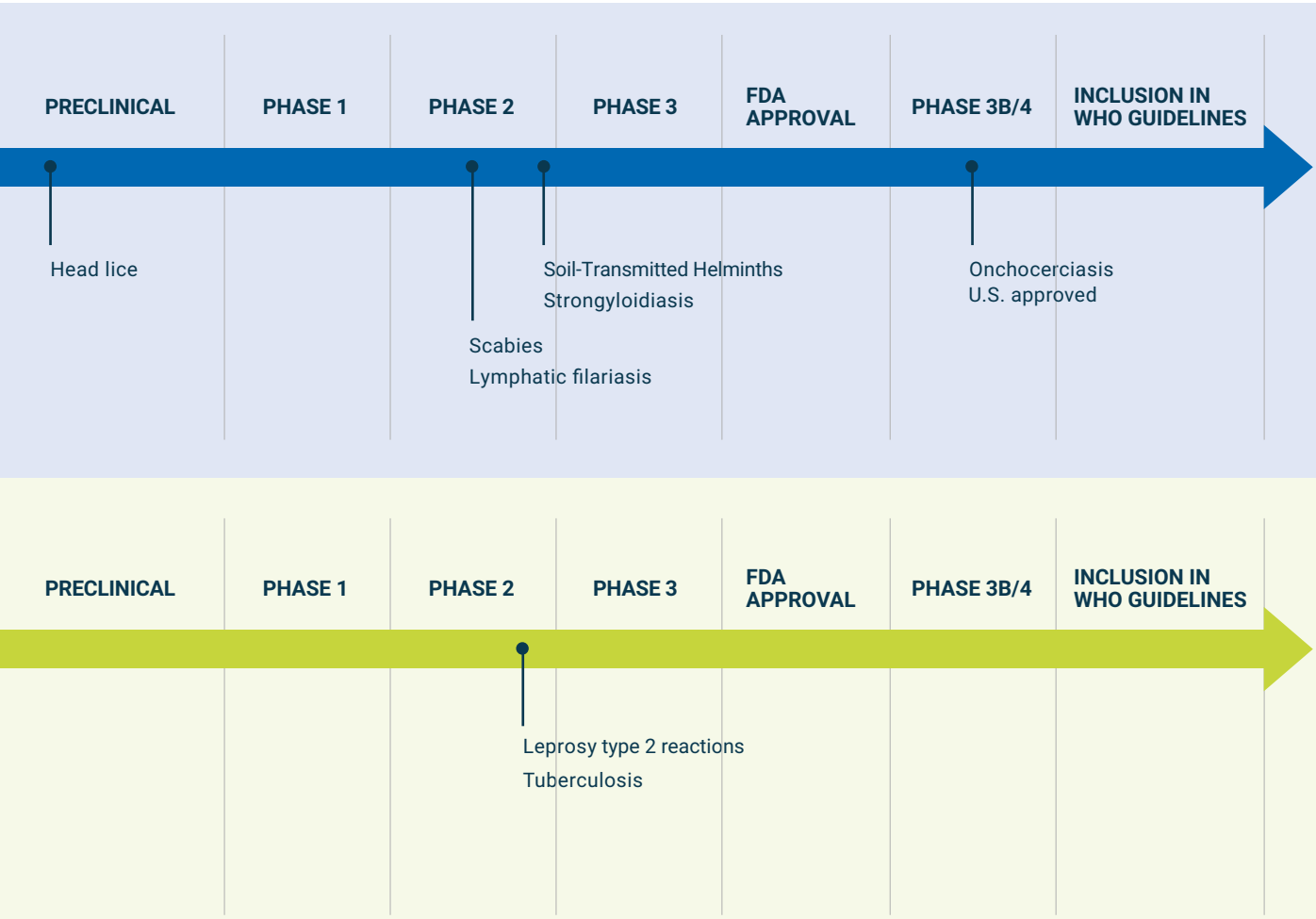
Medicine development progress

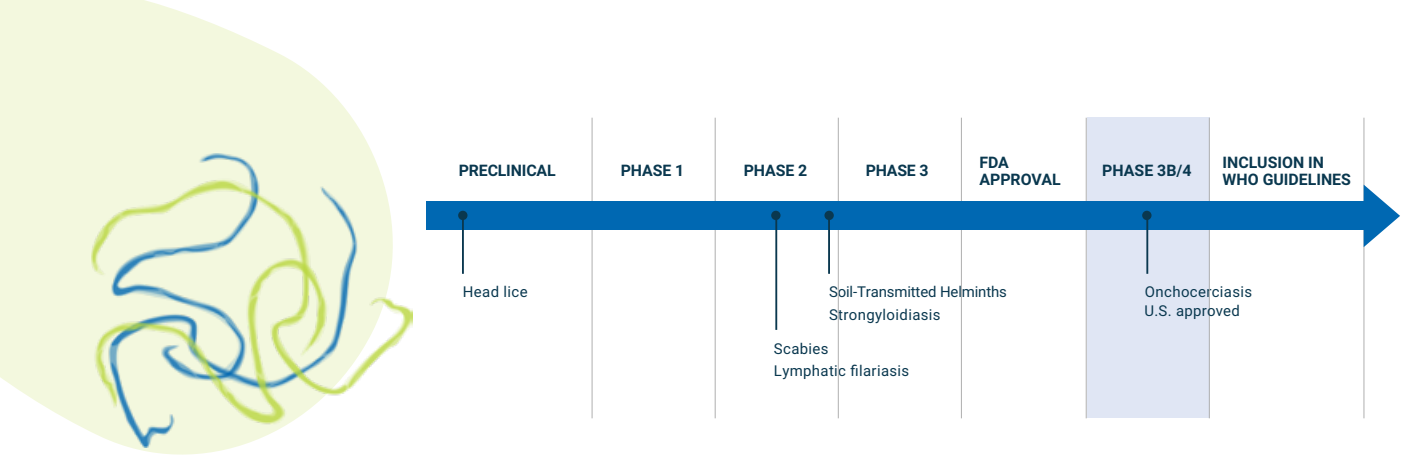
Our expertise is in the product development process, which we apply to advancing medicines and vaccines that address important unmet medical needs, predominantly in low- and middle-income countries. We work with global colleagues, collaborators and contributors at all stages of the process of investigating and implementing new and improved medicines for the treatment of neglected diseases.

Moxidectin

CC-11051
(AMG 634)

Product pipeline





Moxidectin for river blindness

ABOUT RIVER BLINDNESS

River blindness (also known as onchocerciasis) is a neglected tropical disease caused by the parasitic worm *Onchocerca (O.) volvulus*, which is transmitted to humans via bites from infected black flies. The resulting infection can lead to severely debilitating and disfiguring skin conditions, visual impairment and even blindness. More than 200 million people are at risk of infection and almost all infected people live in 31 African countries. Ivermectin is the current standard of care for treating river blindness and has been donated for endemic areas for over 30 years. Still, there are many areas where prevalence is high, and elimination is the long-term goal.

Photo acknowledgement: Gbonjeima, Sierra Leone. Olivier Asselin, 2012.

CLINICAL STUDIES

Medicines Development for Global Health received United States Food and Drug Administration (FDA) approval in 2018 for moxidectin for the treatment of river blindness due to *O. volvulus* for people aged 12 years and older. The company is now working towards inclusion of moxidectin in the World Health Organization guidelines for the management of river blindness. Towards this objective, the company continues to generate data required to implement community-directed treatment with moxidectin in endemic areas.

A repeat-dose trial comparing annual or biannual doses of either moxidectin or ivermectin (MDGH-MOX-3001, NCT03876262; Democratic Republic of the Congo)

This study, which began in early 2021, addresses one of the most important questions in river blindness management: is there merit in increasing the frequency of administration of treatment from annual to biannual as a method of accelerating elimination? It will also provide data on the two treatment options (moxidectin and ivermectin) under these conditions.

The clinical trial continues to recruit despite significant challenges of shifting epidemiology on river blindness (suspected due to deforestation), the need to ensure Covid-safe study operations, as well as to manage intermittent conflict disruptions in the vicinity of study operations in North-Eastern Democratic Republic of Congo. The first patient was enrolled in May 2021. This study is being conducted in conjunction with study MDGH-MOX-3002, outlined on the following page, by a large clinical team who move from village to village. The logistics for community outreach, screening, treatment and assessment are a significant undertaking.

Revisions to the protocol are planned to accelerate the completion of this study. Final recruitment is anticipated by mid-2023.

A single-dose safety study of moxidectin in 12,500 participants (MDGH-MOX-3002, NCT04311671; Democratic Republic of Congo)

This study is being conducted to provide data for World Health Organization's guideline process, evaluating safety in a community setting under conditions typical of a community-directed treatment program. The first person was treated in May 2021. Medicines Development for Global Health is currently assessing the feasibility of bringing on an additional site for the study to accelerate recruitment, and an amendment to include children four to 11 years once a dose for their treatment has been confirmed with data from MDGH-MOX-1006 (see right).

The challenges of running clinical trials while an insurgency is raging all around.

In February 2022, a reporter from the French press agency France 24 ventured into the heart of a conflict zone in the north-eastern province of Ituri, in the Democratic Republic of Congo, where Medicines Development for Global Health is conducting its two clinical trials for moxidectin. The story is a harrowing tale of the challenges of conducting medical research in a time and area of civil strife. It is also a story of the determination of Dr Tony Ukety and his staff to pursue the studies needed to help in the elimination of river blindness in his country.

Read the article

Paediatric study[1] (MDGH-MOX-1006, NCT03962062; Ghana)

Medicines Development for Global Health is conducting a study to establish the dose of moxidectin for children aged four to 17 years of age with (or at risk of) river blindness. The primary objective of the study is to identify an optimal dose for children in two age cohorts: four to seven years of age and eight to 11 years of age. A third cohort of adolescents 12 to 17 years is receiving the United States FDA-approved 8 mg dose to generate further supporting data. The study is being conducted at the School of Public Health, University of Health and Allied Sciences Research Centre, formerly the Onchocerciasis Chemotherapy Research Centre (OCRC) research facility, Hohoe, Ghana.

The initial stage of the study has now been completed and safety and pharmacokinetic data from all three age cohorts in the study are currently being analysed and modelled to confirm the dose of moxidectin. The results of the completed study, supported by the data available from adults, will be the basis of a regulatory application to extend moxidectin's use to include the treatment of children aged four to 11 years. Preliminary results from this study were presented during the American Society of Tropical Medicine and Hygiene's annual meeting in November 2021.

This study is sponsored and funded by Medicines Development for Global Health, and forms part of a broader project supported by grant funding from the European and Developing Countries Clinical Trials Partnership.

Status:

The first adolescents and children were enrolled in April 2021.

Last patient, first visit occured in Q2, 2022. Last patient, last visit is anticipated for Q4, 2022 with the United States New Drug Application supplement dossier submission projected for Q3/Q4 2022.

[1] *American Society of Tropical Medicine and Hygiene 2021 annual meeting. Safety and pharmacokinetics of a single oral dose of moxidectin in subjects aged 4 to 17 years with (or at risk of) onchocerciasis, to identify an optimal dose for treatment of children 4 to 11 years: Early results of an open label study. Opoku N et al. https://app.core-apps.com/tristar-astmh21/abstract/726dfad2-4c98-47e7-9f8c-219f163c0846.*

PAEDIATRIC FORMULATION

Medicines Development for Global Health is working on a paediatric formulation of moxidectin for children under four years of age and others unable to swallow tablets. This will be the first paediatric formulation of a macrocyclic lactone available for global health purposes. The project, also known as "MiniMox", has completed its first year of activity. In the past 12 months, target product characteristics for a paediatric formulation of moxidectin were developed and endorsed by project partners. Professor Hannah Batchelor from the University of Strathclyde, Glasgow, Scotland, commenced research and development work in May 2021 to create two different types of formulations suitable for very young children. These formulations have been developed and manufactured on a small-scale under laboratory conditions, and the project team are now testing these and assessing their stability over time.

In parallel, Professor Joseph Kamgno and his team at the Centre for Research on Filariasis and other Tropical Diseases (CRFilMT), Cameroon, have been conducting community-based surveys of community medicine distributors, children aged three to 12 years of age and their caregivers and other key members of the community. The objective of their study is to assess end-user preferences in medicines used to treat young children. Field work has been completed, and analysis of results is underway.

The outcomes of Professor Batchelor's development work and Professor Kamgno's community surveys will inform final selection of a formulation to be manufactured under international standards of manufacture ('Good Manufacturing Practice') for use as clinical trial material for a relative bioavailability study. This study is planned to compare the paediatric formulation with the approved 2 mg tablet formulation of moxidectin. The relative bioavailability study, MDGH-MOX-1009, is anticipated to commence in 2023.

The "MiniMox" project involves Medicines Development for Global Health Limited in the United Kingdom, an affiliate of Medicines Development for Global Health, Australia; the Luxembourg Institute of Health; the University of Health and Allied Sciences, Ghana; the University of Strathclyde, United Kingdom; the University Hospital Bonn, Germany; and the CRFilMT, Cameroon. The project will benefit from technical and scientific advice from the UNICEF/UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases Research, Switzerland. It is co-funded by the European and Developing Countries Clinical Trials Partnership, the Luxembourg National Research Fund and Medicines Development for Global Health.

Status:

Additional clinical studies

Medicines Development for Global Health is working to provide guidance for the community on moxidectin treatment in breastfed babies and pregnant women using a pharmacokinetic modelling program. Known as a physiologically based pharmacokinetic (PBPK) model, it has been developed specifically for moxidectin using the Simcyp™ PBPK simulator. This model enables the community to better understand how moxidectin is handled by the human body and will help assess risk and benefit of moxidectin in these populations.

The Simcyp simulator uses state-of-the-art in silico technology to model physiologically based pharmacokinetic mechanistic modelling and simulation to predict pharmacokinetic/pharmacodynamic outcomes (PK/PD) in virtual patient populations. This form of modelling is increasingly being used to inform many new drug applications to the FDA, including the support of label claims that do not need clinical trial data, notably claims about drug-drug interactions, dosing regimens, and data about new populations, including paediatrics. Medicines Development for Global Health is leveraging this technology in modelling paediatric dosing for moxidectin.

A Phase 2 clinical study, IIS-MOX-2006 [NCT04049851] in Cameroon assessing the safety of moxidectin in comparison to ivermectin in *Loa loa*-infected individuals is being led by the Institut de Recherche pour le Développement (IRD) and the CRFilMT. This study started in March 2022. Participants will be dosed in two cohorts, and treatment is planned to conclude by July 2022. The final timepoint for analysis is one year post treatment, by June 2023.

PILOT TREATMENT PROGRAMS

World Health Organization's Onchocerciasis Technical Advisory Subgroup endorses pilot treatment programs

Medicines Development for Global Health's core objective is to provide the World Health Organization with the information it needs to judge moxidectin's role in onchocerciasis (and lymphatic filariasis) treatment guidelines. Endemic countries rely on World Health Organization's guidance to frame their own treatment programs. Towards this goal, in December 2021, the World Health Organization's Onchocerciasis Technical Advisory Subgroup agreed on the value of pilot community-directed treatment programs. This comes after ongoing discussions with onchocerciasis experts and a review of moxidectin clinical trial data. The objectives of these pilot programs will be to confirm the safety of moxidectin use in populations living in onchocerciasis-endemic settings and acceptability of moxidectin in affected communities.

These pilot programs can be undertaken in:

- newly identified areas needing to start a treatment program;
- areas where annual or biannual treatment with ivermectin has been ongoing for a long time but more is still needed, particularly in disease "hotspot" areas with significant ongoing transmission that prevent a country from achieving their elimination goals; and
- regions with difficult-to-reach populations, particularly where there is high migratory/cross-border activity.

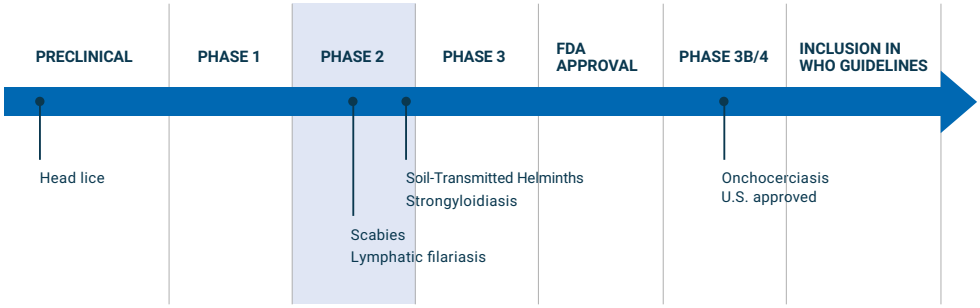
Having received the Onchocerciasis Technical Advisory Subgroup endorsement to proceed, pilot programs are now under discussion with interested countries and program facilitators. An initial project in a border area of South-East Senegal is the first to progress to in-depth meeting discussions and to the planning necessary to successfully deliver treatment and monitor safety outcomes in the target population of approximately 50,000 people. Medicines Development for Global Health is very pleased to be working closely with all stakeholders to ensure the best outcomes for this program and that other demonstration projects are progressed and can benefit from the learnings of this initial pilot program.

It is anticipated that a number of project areas will be confirmed in 2022, progressing to implementation in 2023 and beyond. Medicines Development for Global Health will work with the national regulatory authorities and national onchocerciasis elimination committees of interested countries to confirm importation pathways, develop treatment and surveillance protocols, and – with partners – coordinate to fund supply and logistics.

Modelling studies

Medicines Development for Global Health, working with the Bill & Melinda Gates Foundation, has been in discussion with members of the Neglected Tropical Disease Modelling Consortium. River blindness modelling simulations from both EPIONCHO (Imperial College, London, United Kingdom) and ONCHOSIM (Erasmus University, Rotterdam, Netherlands) have been used to support a business case for the use of moxidectin in onchocerciasis elimination programs. Both models consistently demonstrate that moxidectin would shorten the time to elimination more quickly than ivermectin.

Medicines Development for Global Health is committed to providing moxidectin at no cost to interested countries for these projects.



Moxidectin in lymphatic filariasis

ABOUT LYMPHATIC FILARIASIS

Lymphatic filariasis (also known as elephantiasis) is a painful and debilitating disease caused by a parasitic roundworm (of the family *Filariodidea*) transmitted through the bite of infected mosquitos. Inside the human body, the worms (microfilariae) travel through the lymph system, often undetected, and mature into adult worms that produce millions of microfilariae. Eventually this causes abnormal enlargement of the arms, legs, and (in males) genitalia. According to the World Health Organization, as of 2018 approximately 860 million people in 47 countries live in endemic areas, and over 50 million people are infected with lymphatic filariasis in tropical and sub-tropical regions of Africa, South and East Asia and some Pacific islands. Lymphatic filariasis elimination is targeted by treating whole communities in endemic regions. Current treatment for lymphatic filariasis includes albendazole, either alone or in combination with ivermectin and/or diethylcarbamazine (DEC), depending on the presence of other infections endemic in the region.

Over 50 million people are infected with lympatic filariasis in tropical and sub-tropical regions of Africa, South and East Asia and some Pacific Islands.

CLINICAL STUDIES

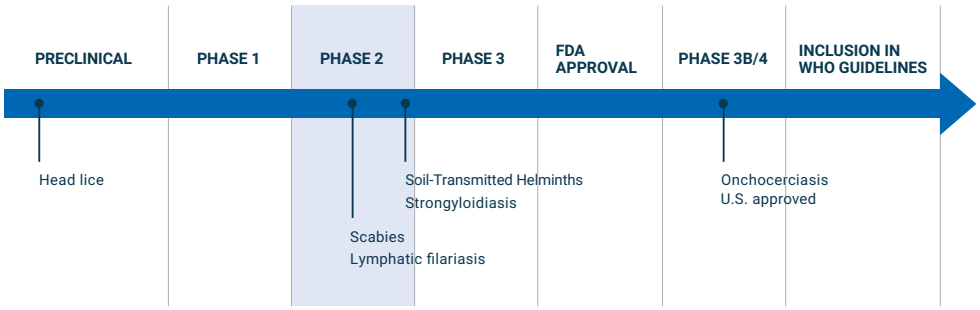
Death to Onchocerciasis and Lymphatic Filariasis (DOLF) project

Preliminary safety and efficacy data from the first clinical trial evaluating moxidectin as a potential treatment option for lymphatic filariasis were presented late last year at the American Society of Tropical Medicine & Hygiene annual meeting in Washington, D.C. The ongoing study, sponsored by the Washington University in St. Louis, USA, as part of the **Death to Onchocerciasis and Lymphatic Filariasis (DOLF) project** is being conducted at the Regional Hospital of Agboville, Southern Cote d'Ivoire. The study is assessing the combination of moxidectin and albendazole or ivermectin and albendazole with and without diethylcarbamazine. It will continue over a further two years, to generate three years of follow-up data after a single treatment. This DOLF project is supported by the Bill & Melinda Gates Foundation.

Status:

Although the data are preliminary and the analysis was of a small subset of the study population, moxidectin combinations were well tolerated and reduced and maintained undetectable microfilaria in blood at 12 months after treatment, compared with similar combination treatment with ivermectin.

Medicines Development for Global Health is now in discussion with advisors, including World Health Organization and the Bill & Melinda Gates Foundation, to evaluate the development pathway regarding the data needed to accelerate a recommendation for treatment of lymphatic filariasis where alternative options are needed.



Moxidectin in scabies

ABOUT SCABIES

Scabies is one of the most common infectious skin conditions with the World Health Organization estimating that, at any one time, more than 200 million people suffer from the disease.

Scabies occurs worldwide and can affect anyone, although the highest rates of infestation are seen in tropical and subtropical climates. The burden of disease is known to be particularly high in Asia, South America and in Australia among our first nations communities. In 2017, scabies was included in World Health Organization's list of neglected tropical diseases.

Scabies is caused by the *Sarcoptes (S.) scabiei var. hominis* mite. Complications from scabies infestations include secondary bacterial skin infections that compound the burden of disease by increasing the risk of nephritis, rheumatic fever, and sepsis. The current treatments for scabies are either topical agents (permethrin and benzyl benzoate) or oral ivermectin. Although topical agents are the most common treatment, the need for them to thoroughly cover and remain on the body for 8-24hrs creates a significant drawback. Oral ivermectin, though more convenient, is only approved for use in a handful of countries and thus is not readily accessible to the majority of people in need. In addition, ivermectin has a short half-life, which usually results in the need for a second dose to be administered to ensure mites from hatching eggs are eliminated. Clearly, there is a need for a widely available, better oral treatment option for scabies.

CLINICAL STUDIES

Proof of concept and dose-finding study

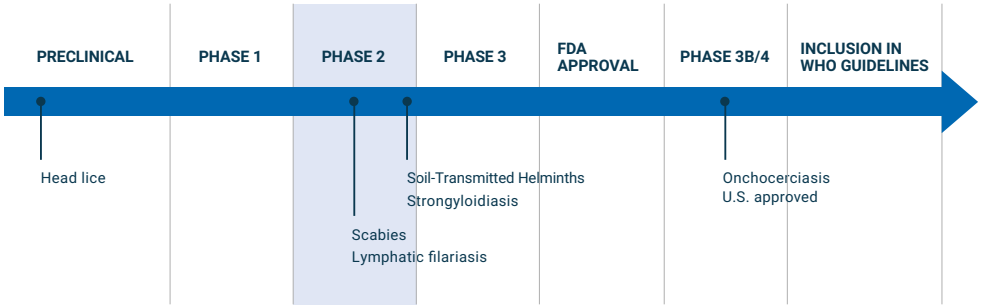
(MDGH-MOX-2001, NCT 03905265)

In January 2020, recruitment began to Medicines Development for Global Health's Phase 2a proof-of-concept and dose-finding study with moxidectin for scabies. The purpose of this early Phase 2a study was to determine the efficacy of moxidectin against human scabies as well as to establish an efficacious moxidectin dose, measuring the impact of differences in moxidectin exposure on *S. scabiei* viability/mortality.

The initial clinical sites were the Hôpital Universitaire Henri Mondor in Créteil, the Centre Hospitalier in Nice and the Centre Hospitalier Universitaire in Saint-Etienne, in France, as well as the Royal Darwin Hospital and Menzies School of Health Research, both in Darwin, Australia. The study was materially impacted by the Covid-19 pandemic, with lockdowns affecting all sites and patients presenting for treatment at hospitals. Despite these difficulties, the site teams maintained their enthusiasm and were able to enrol patients in the study, albeit at a slower rate than originally planned. A fifth site, the Medizinische Universität, in Vienna, Austria, was added to supplement patient recruitment in late 2021 and contributed almost a third of total subjects recruited.

Status:

Recruitment to the study was completed in January 2022 and data are being analysed. These data will be used to inform dose and design of the next clinical study planned for the scabies program, study MDGH-MOX-2002, a Phase 2b dose confirmatory study. The trial will be multinational and the goal is to enrol the first patient by the end of 2022.



Moxidectin in other neglected tropical diseases

SOIL-TRANSMITTED HELMINTHS

The soil-transmitted helminths include roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and hookworm nematodes (*Ancylostoma duodenale* and *Necator americanus*), and are among the most common of all infections with an estimated 1.5 billion people affected worldwide. In the world's poorest communities, these parasitic worms are transmitted through contaminated soil where sanitation is poor. The soil-transmitted helminths infections cause a range of health problems, including abdominal pain, diarrhea, blood and protein loss, rectal prolapse, and physical and cognitive growth retardation. Current treatments recommended by the World Health Organization are albendazole and mebendazole.

STRONGYLOIDIASIS

Strongyloidiasis is caused by *Strongyloides stercoralis.* Unlike other soil-transmitted helminths, *S. stercoralis* has a different lifecycle and the infection it causes can be fatal. The World Health Organization estimates that up to 100 million people, particularly children, are infected with this parasitic worm. Treatment options are limited, with ivermectin being the medicine of choice, while other anthelmintic medicines, such as albendazole and mebendazole, lack sufficient efficacy as a single agent.

CLINICAL STUDIES

Soil-transmitted helminths studies

A previous investigator-led study, published in 2020 (Keller et al., *Clinical Infectious Diseases* 2020, 70 (6); 1193–1203) concluded that moxidectin plus albendazole was superior to moxidectin in adolescents with whipworm, and confirmed a moxidectin dose of 8 mg used in combination with albendazole should be further investigated for the control of the soil-transmitted helminths.

Medicines Development for Global Health has collaborated in two recently completed Phase 2 clinical trials in soil-transmitted helminths (whipworm), both conducted by the Swiss Tropical and Public Health Institute, Switzerland:

In Tanzania (NCT04700423): the study included 5 different regimens: moxidectin plus albendazole, ivermectin plus albendazole, albendazole monotherapy, ivermectin monotherapy, or moxidectin monotherapy in adolescents aged 12–19 with whipworm.

In Cote d'Ivoire (NCT04726969): the study compared moxidectin plus albendazole, albendazole, and ivermectin plus albendazole in adolescents or adults (ages 12–60) with whipworm.

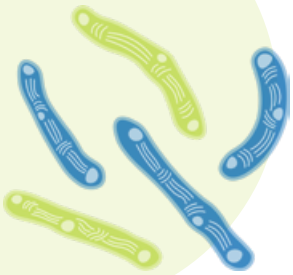
Status:

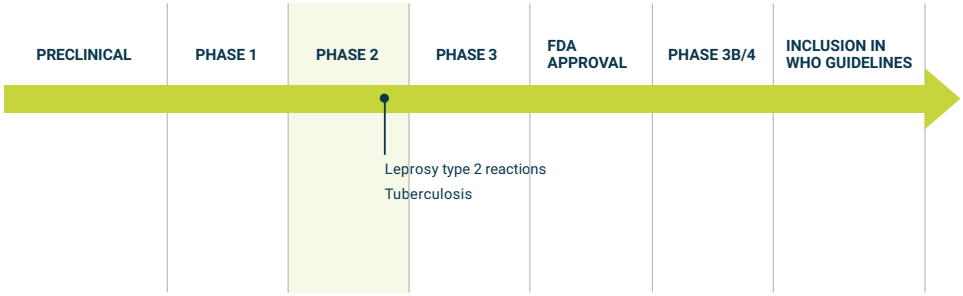
Both studies are expected to be published soon.

Strongyloidiasis studies

In 2021, initial results from one investigator-led study, evaluating ascending doses of moxidectin, was published in *The Lancet Infectious Diseases* (Hofmann D. et al. *Lancet Infect Dis* 2021 21 (8); 1151–1160) and recommended that 8 mg moxidectin should be used for future trials for strongyloidiasis therapy.

Medicines Development for Global Health is collaborating with the Swiss Tropical and Public Health Institute, Switzerland, on clinical trials in Cambodia and Laos to assess the efficacy of moxidectin compared to ivermectin in adults infected with *S. stercoralis*.





CC-11050 in leprosy type 2 reaction

ABOUT LEPROSY AND LEPROSY TYPE 2 REACTION

Leprosy, also known as Hansen's Disease, remains a devastating condition. According to the World Health Organization, 127,558 new cases of leprosy were registered in 2020 across 139 countries from the six World Health Organization regions, with the largest number of cases in India, followed by Indonesia and Brazil. Caused by slow-growing *Mycobacterium leprae* bacteria, leprosy may take up to 20 years before signs of infection affect nerves, skin, eyes, or the lining of the nose.

Around 30 to 50% of leprosy patients also develop leprosy type 2 reaction, also known as erythema nodosum leprosum. This condition is an immune-mediated and severe complication of leprosy, which can affect people with active leprosy infection, as well as those that have been effectively cured with multidrug therapy, even many years later. Leprosy type 2 reaction is a "multisystem, relapsing and remitting disorder" caused by residual antigenic remnants, not the *M. leprae* bacteria itself. While the underlying immunologic mechanisms of leprosy type 2 reaction may not be fully understood, the inflammatory responses can cause morbidity and mortality if not treated in a timely manner.

Leprosy type 2 reaction is associated with clinical presentations such as skin lesions, nerve pain, joint pain, and inflammation of the eye, bone, lymph nodes and kidneys. It is treated mainly with corticosteroids, which are often required for extended periods of time, resulting in toxicity for the patients.

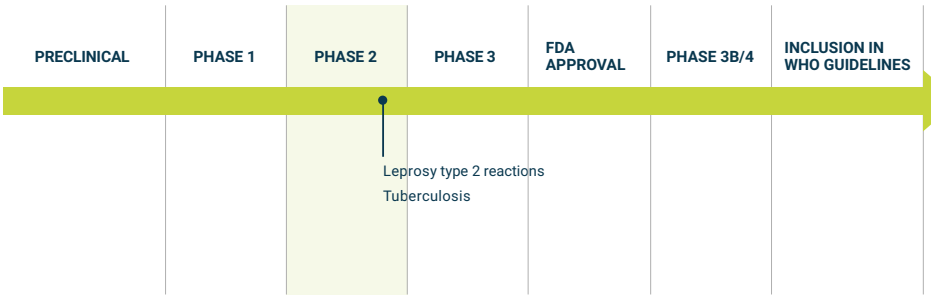
Even after successful treatment with antibiotics that eradicate the bacteria, the immune system reactions persist for years. While steroids remain the standard of care in treating leprosy type 2 reaction as well as the occasional use of thalidomide, new and safer alternatives are being sought.

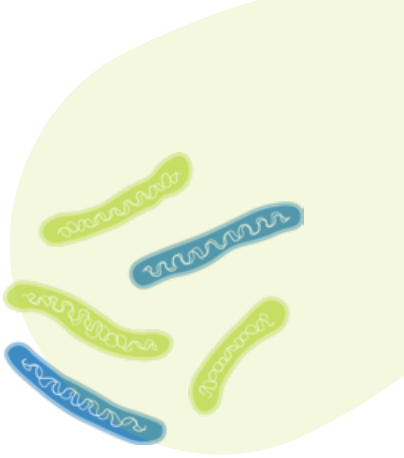
Research status:

The first part of a two-part Phase 2 clinical trial in patients treated with CC-11050 has been completed in Leprosy Mission's Anandaban Hospital in Nepal. The results of this first study in 10 patients demonstrated a consistent effect of CC-11050 treatment. Part two of this study, funded by Amgen Inc., involves approximately 40 patients treated over a longer duration. This was on hold in 2021 due to conversion of the leprosy hospital to a Covid-19 clinic but the study is planned to commence towards the end of 2022.

In addition, a clinical trial sponsored by Medicines Development for Global Health is being designed to confirm the optimal dose of the improved formulation of CC-11050 and compare efficacy and safety to the current standard of care, prednisolone. The trial will be a collaboration with colleagues at Institut Pasteur and Institut Raoul Follereau, and is planned to be conducted in West Africa and the United States in late Q4 2022.

A pre-investigational new drug application meeting with the FDA is scheduled for mid-2022, with Medicines Development for Global Health preparing a dossier to discuss plans for CC-11050 in the areas of manufacturing, non-clinical safety, and toxicology, as well as clinical trial design.





CC-11050 in tuberculosis

CC-11050 is an anti-inflammatory compound being investigated as a potential treatment for leprosy type 2 reactions and tuberculosis.

ABOUT TUBERCULOSIS

Tuberculosis is a disease caused by the bacteria *Mycobacterium tuberculosis*. The infection primarily affects the lungs, but can disseminate to any part of the body, such as the kidney, spine, and brain. Despite being both a preventable and curable disease, it is the second leading infectious disease killer after Covid-19, with 10 million new cases and 1.4 million deaths reported in 2019. While tuberculosis is global, most people who contract tuberculosis are in low and middle-income countries.

Current antibacterial therapeutic regimens for tuberculosis are complex, requiring patients to undergo daily multidrug treatment for 6 months and, in some cases, up to two years. Multidrug-resistant tuberculosis remains a public health emergency: of the 10 million new cases in 2019, over 200,000 were multidrug-resistant. In addition, the antimicrobial treatment of *Mycobacterium tuberculosis* can result in damaging inflammation, leaving permanent damage in some patients.

The role of the immune system is critical in tuberculosis pathogenesis. *Mycobacterium tuberculosis* can live in the body without causing disease (latent tuberculosis infection) but can reactivate, particularly in those with weakened immune systems. While antibacterial strategies are generally effective against tuberculosis, there are few immunomodulatory treatments to limit damage during the treatment process. CC-11050, a novel immunomodulator from the PDE-4 class, has shown promising preliminary results, published in *The Lancet Respiratory Medicine* in March 2021, improving markers of lung function in those receiving concurrent treatment.

Research status:

A Phase 2 randomised controlled trial [AUR-1-313-DRtuberculosis-HDT] of two adjunctive host-directed therapies (CC-11050 and metformin) in rifampin-resistant tuberculosis commenced early in 2022. The study sponsor is the Aurum Institute, South Africa, and 330 subjects are planned to be enrolled at sites in South Africa, Mozambique, Germany, Romania, Georgia, and Moldova.

Annual achievements & highlights

Neglected Tropical Diseases (NTDs) and tuberculosis affect the lives of one out of every five people on the planet. Medicines Development for Global Health continues in its efforts to tackle neglected diseases and to have a positive impact on the lives of those who can least afford new medicines.

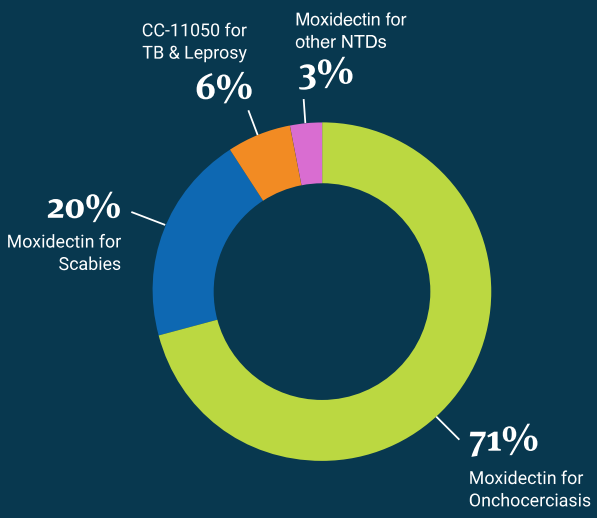
Financials

As a not-for-profit organisation registered with the Australian Charities and Not-for-profits Commission (ACNC) and endorsed as a Deductible Gift Recipient (DGR, type1), Medicines Development for Global Health has relied on two major funding streams: the proceeds from the sale of our priority review voucher as well as the generous support from public sector government and private funding bodies. Among the currently active public sector funding received by Medicines Development for Global Health are support from the European and Developing Countries Clinical Trials Partnership and the Luxembourg National Research Fund for the ongoing clinical trial programs for moxidectin. Private funding across multiple Medicines Development for Global Health programs come from Atticus Medical Pty Ltd, the Bill & Melinda Gates Foundation and funding from entities for which Medicines Development for Global Health provides development management support services, such as the Murdoch Children's Research Institute.

With an expanding clinical trial portfolio, the need to expand beyond the existing sources of funding becomes critical for ongoing development success for Medicines Development for Global Health. In 2021, Medicines Development for Global Health accelerated a corporate effort to take greater advantage of the opportunities afforded the organisation through the larger pool of public sector governmental support, private funding sources, impact investment, and blended finance mechanisms. New outreach efforts have already begun in Australia and will soon be expanded to reach out to both North American and additional European sources of funding. The expansion of operations in both the United Kingdom and United States is just one of the steps being taken by Medicines Development for Global Health to address those additional philanthropic opportunities. Please see page 22 for more information.

USE OF R&D FUNDS, 2021

Medicines Development for Global Health's use of funding for research and development activities in 2021 is shown below.



Detailed financial reports, including audited financial statements, are available on the ACNC website.

Awards and recognitions

Mark Sullivan appointed an Officer of the Order of Australia

In February 2022, Mark Sullivan, Founder and Managing Director of Medicines Development for Global Health, was appointed an Officer of the Order of Australia (AO), one of the highest civilian honours in Australia. Instituted in 1975 by Queen Elizabeth, the Sovereign Head of Australia, the award is an Australian society honour that recognises "distinguished service of a high degree to Australia or humanity at large."

On receiving the Officer of the Order of Australia award, Mark Sullivan said:

"This is a wonderful recognition of our work at Medicines Development for Global Health, and it is particularly meaningful as the nomination for the Order of Australia comes from our peers. But this award belongs to us all at Medicines Development for Global Health, as well as our partners, collaborators, and supporters. It is their outstanding efforts and tireless work that have made this possible. The recognition of those efforts is, indeed, an honour."

MDGH nominated for Prix Galien Award

Medicines Development for Global Health and its collaborators at TDR, the Special Programme for Research and Training in Tropical Diseases (co-sponsored by the United Nations Children's Fund, the United Nations Development Programme, the World Bank, and the World Health Organization) were, once again, honoured by the Galien Foundation with a nomination for moxidectin for Best Pharmaceutical Product at the 2021 Prix Galien Awards.

The aim of this prestigious annual award is to promote significant advances in pharmaceutical research. A prominent jury, including clinicians, toxicologists, pharmacologists, and pharmacists, is brought together each year to vote on award nominees. The award gives credit to the most important medicines introduced into the public market as well as to the achievements of the best research team in the pharmaceutical field. It is considered the pharmaceutical industry's equivalent of the Nobel Prize and the highest accolade for research and product development.

Outreach efforts

As clinical trial efforts continue for both moxidectin and CC-11050, Medicines Development for Global Health is being more proactive in disseminating information about its clinical development pipeline as well as the organisation itself. These efforts are designed to increase awareness of Medicines Development for Global Health and its activities across the broad spectrum of the global public health community, from regulators to donors, from implementation partners to those in governmental and non-governmental offices. This awareness of new medicines will be critical to ultimate approval and field implementation.

To expand awareness of the organisation and to continuously update its development programs, in 2021 we published the first annual report of the company, launched quarterly newsletters, refreshed our website, participated in several key international scientific meetings, and our scientists published high impact papers.

There are two main streams of activities for these efforts: corporate communications, and medical affairs/scientific advisory outreach.

In 2021, Medicines Development for Global Health convened the first two in an ongoing series of scientific advisory meetings, inviting key opinion leaders to share their critical thinking and experiences related to the future planning efforts for moxidectin for river blindness. These groups, representing academia, clinical development, pharmaceutical manufacturing, governmental and non-governmental bodies, and funders, have provided valuable insights as Medicines Development for Global Health evaluates the implications of implementation efforts for moxidectin for river blindness.

The company is collaborating with Global Institute for Disease Elimination (GLIDE), the Abu Dhabi-based organisation, in the planning stages of a summit aimed at addressing the critical need for sustainable financing for essential medicines and diagnostics to treat neglected tropical diseases. The late-2022 meeting will bring together stakeholders involved in the development, supply, distribution, implementation and funding of neglected tropical disease medicines, to critically evaluate the current financing models and supply models for health technologies, and to propose alternative funding solutions to ensure sustainable impact to patients.

Below are examples of engagement activities with several global health organisations:

Global Institute for Disease Elimination (GLIDE)

Based in Abu Dhabi, GLIDE was established through a partnership between His Highness Sheikh Mohamed bin Zayed Al Nwahyan, The Crown Prince of Abu Dhabi, and the Bill & Melinda Gates Foundation. MDGH is working with GLIDE on a series of engagement and advisory meetings to provide technical and organisational support.

Bridges to Development

Medicines Development for Global Health is working with the Seattle and Geneva-based team at Bridges to Development to assist with implementation planning for moxidectin.

The END Fund and Sightsavers

Medicines Development for Global Health is working with both organisations to identify and coordinate pilot treatment programs across a number of sub-Saharan countries..

Uniting to Combat Neglected Tropical Diseases

Medicines Development for Global Health officially joined the Uniting to Combat Neglected Tropical Diseases group and is working with the entity on the company's commitments to the Kigali Declaration.

OUTREACH FOCUS

The addition of CC-11050 to the Medicines Development for Global Health portfolio marked a new era in the company's growth. Significant outreach efforts were underway in 2021 to shape future development of the investigational medicine as well as outreach with funders. Medicines Development for Global Health raised social impact investment for its work on leprosy type 2 reaction and tuberculosis against the potential award of a priority review voucher. The new funding will be used for CC-11050 development activities leading towards pivotal clinical trials, including new formulation work, manufacturing, and additional nonclinical safety and toxicology studies.

Partnership in action

The core focus for Medicines Development for Global Health has and always will be developing medicines. Prior to 2014, however, when the World Health Organization asked MDGH to take on development efforts for moxidectin, all activities of the company were in support of the development efforts of other organizations. While Medicines Development for Global Health continues to focus its main efforts on the development of both moxidectin and CC-11050, a part of the team continue to collaborate in development programs for other sponsors.

One long-standing and productive collaboration was honoured last year in the awarding of the 2021 Eureka Prize for Infectious Disease Research to Professor Julie Bines, Murdoch Children's Research Institute and University of Melbourne, for her work leading the development of a new rotavirus vaccine for newborns. The Australian Museum Eureka Prizes are among the country's most prestigious national science awards, honouring excellence across the areas of research and innovation, leadership, science engagement, and science in schools. Medicines Development for Global Health's own Amanda Handley, MPH, Head of Development Management, was a key member of Professor Bines' team, spearheading the group's efforts to develop a safe, effective, and affordable vaccine that will prevent rotavirus gastroenteritis from birth, potentially saving thousands of lives.

Looking forward

Medicines Development for Global Health's global presence

Medicines Development for Global Health, Inc.

Medicines Development for Global Health has been working closely for some time with a large number of key contributors in the Americas. Headquartered in New Jersey, Medicines Development for Global Health, Inc., our United States company, builds on a longstanding presence of advisors and partners in New York and New Jersey, where current global outreach efforts are based. The company's focus will be to create an even stronger presence in the global health sector in the Americas.

The Board members for Medicines Development for Global Health, Inc. include three members of the Medicines Development for Global Health board in Australia, Dr. Lorna Meldrum (Chair), Professor Mark Sullivan AO and Professor Andrew Wilks (University of Melbourne; Co-Founder and Executive Chairman of SYNthese Med Chem). The two United States-based directors are Lawrence V. Stein (former Executive Vice President, General Counsel and Corporate Secretary at Celgene Corporation; former Senior Vice President and General Counsel at Wyeth Corp.) and Dr. Joseph Camardo (former Senior Vice President and Head of Global Health at Celgene Corp.; former Senior Vice President of Global Medical Affairs and Senior Vice President of Clinical Research and Development at Wyeth Corp.).

Medicines Development for Global Health Inc. is a tax-exempt 501(c)(3) public charity.

Medicines Development for Global Health, Limited

Medicines Development for Global Health Limited was established in the United Kingdom in 2015. Late in 2021, the United Kingdom company announced the appointment of two additional directors, Dr Michael Elliott (FRCP; Vice President of Australia, Canada, Europe Medical Affairs at Gilead Sciences in London) and Professor Andrew Wilks (University of Melbourne; Co-Founder and Executive Chairman of SYNthesis Med Chem). These new directors join the existing members of Medicines Development for Global Health Limited Board of Directors: Kate Antrobus (Board Chair, Chief Investment Officer at Univercells), Dr. Lorna Meldrum and Mark Sullivan, AO..

The company applied for registration with the Charity Commission for England and Wales.

Global board of directors

Mark Sullivan, AO
Managing Director, Global
Chair of the Board, US

Lorna Meldrum, PhD
Chair of the Board, AU
Director, UK, US

Andrew Wilks, PhD
Director, Global

Kate Antrobus, MPA, CFA
Chair of the Board, UK

David McGregor
Director, AU

Richard Fiora
Director, AU

Daren Armstrong
Company Secretary, AU

Michael Elliot, FRCP
Director, UK

Lawrence V. Stein
Director, US

Joseph Camardo, PhD
Director, US

Acknowledgements

The path to introduce a new medicine into the community is one of the most complex human endeavours and involves many steps and many more hands, hearts, and minds.

It is a process that Medicines Development for Global Health could not do without the support, cooperation and collaboration of many people and organisations. It is an ever-growing list that is far too long to record. Yet there are some individuals and organisations that we would be remiss in not acknowledging for their extraordinary efforts that have been fundamental to achievement of Medicines Development for Global Health's progress to date.

OUR PARTICULAR THANKS TO:

- The European and Developing Countries Clinical Trials Partnership and the Luxembourg National Research Fund for their ongoing support of the moxidectin paediatric formulation project and implementation programs. These projects are part of the EDCTP2 programme supported by the European Union (grant number RIA2017NCT-1843-MoxiMultiDoseMod and grant number RIA2019PD-2880-MiniMox).
- Dr Annette Kuesel, an inspirational public health scientist, and Dr John Reeder, whose leadership and enabling have made this all possible: both from TDR, the UNICEF/UNDP/World Bank/World Health Organisation Special Programme for Research and Training in Tropical Diseases (Switzerland).
- In addition to Annette Kuesel, we thank the following people and organisations working with us on the moxidectin paediatric formulation project:
  - Professor Hannah Batchelor, The University of Strathclyde, Glasgow, (Scotland)
  - Prof Achim Hoerauf and Dr Kenneth Pfarr, the University Hospital Bonn (Germany)
  - Dr Nicholas Opoku, the University of Health and Allied Sciences (Ghana)
  - Professor Joseph Kamgno, the Centre for Research on Filariasis and other Tropical Diseases (CRFilMT; Cameroon).
- Dr Michel Vaillant and Adriana Voicu from the Luxembourg Institute of Health for their coordination of the collaborations with European and Developing Countries Clinical Trials Partnership.
- Dr Tony Ukety, Dr M. Mandro and the Centre de Recherche en Maladies Tropicales (CRMT) de l'Ituri, Democratic Republic of the Congo, for their conduct of the MDGH-MOX-3001 and MDGH-MOX-3002 clinical trials.
- Dr Nicholas Opoku and the School of Public Health, University of Health and Allied Sciences, Volta Region, Ghana, for supervision and conduct of the MDGH-MOX-1006 clinical trial.
- Dr Christy Hanson, Deputy Director, Neglected Tropical Diseases, her colleagues Dr Rachel Bronzan, Dr Jordan Tappero and Dr Janet White, and numerous others at the Bill & Melinda Gates Foundation for their generous support and funding to Medicines Development for Global Health for ongoing moxidectin development programs.
- The team at Amgen Inc. for their support of our work and efforts to foster the development of CC-11050 for public health benefit in both leprosy and tuberculosis.
- The team at the Leprosy Mission Nepal for their efforts on the CC-11050 leprosy type 2 reaction clinical study, including Dr Deanna Hagge.
- Daren Armstrong, Jeanette Hoogstad and Jackson Harrison at Banki Haddock Fiora.
- Dr Gilla Kaplan, another tireless pubic health scientist, devoted to positive impact on peoples' lives.
- Professors Wilma A. Stolk, María-Gloria Basáñez and teams for their efforts on the modelling of elimination of onchocerciasis.
- Professor Robert Wallis and the team at the Aurum Institute for their efforts on the ongoing study in tuberculosis.

- Thank you to our colleagues at the neglected tropical disease Modelling Consortium at Imperial College, London, United Kingdom, and Erasmus University, Rotterdam, The Netherlands, for their collaborative efforts.
- Dr Gary Weil and his colleagues from the Death to Onchocerciasis and Lymphatic Filariasis (DOLF) project at Washington University, St. Louis, USA, for their ongoing moxidectin research efforts in lymphatic filariasis in Côte d'Ivoire.
- Dr Julie Jacobson, Bridges to Development, for ongoing technical support.
- Professor Jennifer Keiser from the Swiss Tropical and Public Health Institute on the ongoing collaboration on moxidectin in soil transmitted helminths.
- Simon Bland and Dr. Aïssatou Diawara at the Global Institute for Disease Elimination for their collaborative efforts in preparing an innovative financing summit to identify sustainable solutions for the supply of medicines and diagnostics for neglected tropical diseases.
- Cedric Chesnais and all at Institut de Recherche pour le Développement for ongoing collaboration for evaluating the safety and efficacy of moxidectin in Loa loa endemic areas.
- We thank the following impact investors for their support which facilitated the successful initiation of CC-11050 development activities at Medicines Development for Global Health:
  - Lyrebird Charitable Fund
  - Wolf Capital Pty Ltd
  - The Tegmen Fund Pty Ltd
  - Salt Catalyst Pty Ltd
  - Roberts Family Foundation Pty Ltd
  - Alyse Pty Ltd and Este Louise Darin Cooper Pty Ltd
  - Isaacson Davis Foundation
  - Michael & Janet Buxton Foundation
  - Australian Philanthropic Services Foundation Pty Ltd
  - Spinifex Pty Ltd
  - Gaudry Foundation Pty Ltd
  - Height Morris Foundation
  - I and D Gust Family Trust.

Medicines Development for Global Health is deeply grateful to you all for your investment of time and resources, and to your shared commitment to improving public health.

Photo: © World Health Organization. Photographer: Diego Rodriguez, 2015. Subject: people bathing in a canal near Nyaungshwe, Myanmar.

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ABN: 79 116 977 523

2021

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Medicines Development for Global Health acknowledges the Yalukit Willam Peoples of the Boon Wurrung, the First Peoples of Country on which the company's headquarters stands. We pay our respects to all the world's First Peoples, to their ancestors and Elders, and to our shared future.