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PROPOSAL FOR THE INCLUSION OF MOXIDECTIN

IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES AND THE MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN

FOR THE TREATMENT OF ADULTS AND CHILDREN WITH ONCHOCERCIASIS AND LYMPHATIC FILARIASIS

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1. SUMMARY STATEMENT OF THE PROPOSAL

This submission is made in support of the inclusion of moxidectin in the core List of Essential Medicines (EML) and List of Essential Medicines for Children (EMLc), for the treatment of two filarial diseases, onchocerciasis and lymphatic filariasis. A square box listing is proposed for moxidectin as a therapeutic alternative to ivermectin within the anti-filarial class of medicines.

Onchocerciasis, caused by the filarial nematode *Onchocerca (O.) volvulus*, and lymphatic filariasis caused by *Wuchereria (W.) bancrofti* and *Brugia* species affect hundreds of millions of people worldwide. Onchocerciasis, or river blindness, is associated with severe visual impairment and skin disfigurement. Lymphatic filariasis can result in debilitating irreversible lymphoedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions and are co-endemic in many regions of Africa. The World Health Organisation (WHO) road map for neglected tropical diseases 2021-2030(1) targets both onchocerciasis and lymphatic filariasis for elimination.

Despite substantial progress with current treatment strategies, in 2022, approximately 246 million people still required preventive chemotherapy against onchocerciasis(2) and 794 million people required preventive chemotherapy against lymphatic filariasis(3).

Moxidectin has clinically demonstrated advantages over ivermectin with the potential to accelerate elimination of both diseases, enabling cost savings for implementing countries, and allowing for the integration and streamlining of lymphatic filariasis and onchocerciasis elimination programmes in co-endemic settings.

This submission outlines how incorporating moxidectin into the EML and EMLc will support access to a valuable new medicine to support ongoing disease elimination efforts and to improve health outcomes for millions of individuals in endemic regions.

2. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

Medicines Development for Global Health (MDGH) consulted with the WHO Department of Control of Neglected Tropical Diseases (NTDs) in the development of this application. Details of the key focal points involved in this consultation are provided below.

Dr Maria Rebollo Polo
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Review of this submission by the WHO EML Secretariat is expected to run in parallel with a Department of Control of NTD-led review of WHO treatment guidelines for onchocerciasis and lymphatic filariasis. It is anticipated that moxidectin will be considered for inclusion in these guidelines. In September 2024, the key people listed above were invited to review and provide feedback on the draft submission prepared by MDGH to ensure alignment with WHO strategies and priorities.

3. OTHER ORGANISATIONS CONSULTED AND/OR SUPPORTING THE SUBMISSION

Apart from the WHO consultation described in Section 2, MDGH developed this submission independently.

Letters from organisations and individuals who support the submission but did not participate in its development are included in Annex 1. A list of those providing a letter of support is provided below.

Table 1: Letters of support for EML/EMLc submission

Name	Role and Organisation	Page
Dr. Franklin Asiedu-Bekoe	Director Public Health, Ghana Health Service	36
Professor Lydia Aziato	Vice Chancellor, University of Health and Allied Sciences, PMB 31, Ho, Volta Region, Ghana	37
Dr. Paul T. Cantey	Chief, Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, U.S. Centers for Disease Control and Prevention	39
Mr. Simon Bland	Chief Executive Officer, Global Institute for Disease Elimination	41
Dr. Michel Boussinesq	Director of Research, Institut de Recherche pour le Développement, France	43
Mr. Simon Bush	Director Neglected Tropical Diseases, Sightsavers	45
Professor Achim Hörauf	Director, Institute of Medical Microbiology, Immunology and Parasitology (IMMIP) Coordinator, Bonn-Cologne Site, German Center for Infectious Disease Research (DZIF) Speaker of the German Network against Neglected Tropical Diseases, Universitatsklinikum Bonn	46
Professor Joseph Kamgno	Higher Institute for Scientific and Medical Research, Cameroon	48
Dr. Patrick Lammie	Director, Neglected Tropical Diseases Support Center, The Task Force for Global Health	49
Professor John Reeder	Director, Department of Research for Health and Director, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization	51
Ms. Jamie Tallant	Associate Vice President and Team Lead for the Reaching the Last Mile Fund, The End Fund	52
Dr. Tony Ukety	Medical Director, Centre De Recherche En Maladies Tropicales, Democratic Republic of Congo	54

4. KEY INFORMATION SUMMARY FOR THE PROPOSED MEDICINE

A summary table is provided below for each indication for which moxidectin is proposed for inclusion.

4.1 Moxidectin for Onchocerciasis Summary Table

Table 2: Moxidectin for onchocerciasis summary table

INN	Moxidectin		
ATC code	P02CX03		
Indication	Treatment of onchocerciasis in adults and children aged 4 years and older		
ICD-11 code	1F6A - Onchocerciasis due to *Onchocerca volvulus*		
Dosage form	**Strength**	**EML**	**EMLc**
Tablet	2mg	Yes	Yes

4.2 Moxidectin for Lymphatic Filariasis Summary Table

Table 3: Moxidectin for lymphatic filariasis summary table

INN	Moxidectin		
ATC code	P02CX03		
Indication	Treatment of lymphatic filariasis in adults and children aged 4 years and older		
ICD-11 code	1F66.3 – Lymphatic filariasis		
Dosage form	**Strength**	**EML**	**EMLc**
Tablet	2mg	Yes	Yes

4.3 Paediatric Quality Product Profile Assessment

In November 2023, the WHO hosted Global Accelerator for Paediatric formulations (GAPf) network paediatric drug optimisation (PADO) initiative released the first ever list of priority paediatric formulations for five neglected tropical diseases to target research and development to address the specific needs of infants and children(4). Moxidectin for onchocerciasis and scabies was included as a priority in this list, reinforcing the public health need for this population.

A systematic assessment of the age-appropriateness of moxidectin 2 mg tablets for children has been performed using the WHO paediatric quality product profile assessment tool (pQPPAT). This assessment is included in Annex 2: WHO paediatric quality product profile assessment tool (pQPPAT) . A supplemental New Drug Application (sNDA) was submitted by MDGH to the United States (US) Food and Drug Administration (FDA) in August 2024 to expand product labelling of moxidectin for onchocerciasis to include children aged 4 to 11 years old. A decision by the US FDA is anticipated by approximately March 2025, prior to the meeting of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines. The completed pQTPP assessment is based on anticipated US FDA labelling from March 2025. A full application for registration of moxidectin for the treatment of onchocerciasis in children (4 years and older) and adults has been submitted to the Ghana Food and Drug Authority (WHO Maturity level 3). This application contains the same data as submitted to the US FDA in the initial application and the sNDA for children less than 12 years. The outcome of this application is expected by end of 2024.

Data from a Phase 2 study led by the Washington University in St Louis (hereafter referred to as study NCT04410406) indicates that the same moxidectin 8 mg dose as is indicated for treatment of onchocerciasis has a similar safety profile with superior efficacy to ivermectin when used in combination with albendazole +/- diethylcarbamazine for treatment of lymphatic filariasis in adults. Preliminary results of study NCT04410406 are provided in Section 8.4. The safety of moxidectin for

use in children aged 4 years and older living in areas co-endemic for onchocerciasis and lymphatic filariasis is being evaluated in an ongoing clinical trial (hereafter referred to as MDGH-MOX-3002), as outlined in Section 8.5. Results from this study are expected to be available by March 2025, prior to the meeting of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines.

5. LISTING AS AN INDIVIDUAL MEDICINE OR AS REPRESENTATIVE OF A PHARMACOLOGICAL CLASS OR THERAPEUTIC GROUP

This application proposes that a square box symbol (□) is used to indicate that moxidectin is an acceptable therapeutic alternative to ivermectin for the treatment of onchocerciasis and lymphatic filariasis.

Both ivermectin and moxidectin are of the macrocyclic lactone class of anthelminthics. Moxidectin has demonstrated superior efficacy and comparable safety to ivermectin for treatment of onchocerciasis and lymphatic filariasis in clinical trials. However, comparative effectiveness in real-world settings has not yet been fully established. For this reason, ivermectin has been proposed as the listed representative for selection at the national level, with moxidectin as the acceptable therapeutic alternative.

6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

6.1 Global Disease Burden

Onchocerciasis (river blindness) is a debilitating and stigmatizing disease caused by the parasitic helminth *Onchocerca (O.) volvulus*. *O. volvulus* larvae are transmitted through the bites of black fly species and can develop into mature adult worms (macrofilariae). These adults become encapsulated in skin and deep tissue nodules, from which they release millions of microfilariae that migrate through the skin and eyes. The resulting infection causes a chronic host immune response that can lead to visual impairment (and, in some cases blindness), severe itching, and debilitating and disfiguring skin disease. Both dermal and ocular manifestations have serious social and economic consequences, both to the individual and their communities. These diseases compound poverty, undermine development in endemic countries, and justify the vigorous efforts being made to control the disease.

Onchocerciasis occurs mainly in tropical areas(5). The vast majority of infected people live in sub-Saharan African countries: Angola, Burkina Faso, Burundi, Cameroon, Chad, Congo, Cote D'Ivoire, Central African Republic, Democratic Republic of Congo, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Liberia, Malawi, Mali, Nigeria, Tanzania, Togo, South Sudan, Sierra Leone, Senegal, Sudan, and Uganda. Onchocerciasis is also transmitted in Brazil and Venezuela (Bolivarian Republic of), as well as in Yemen(2,5).

Latest estimates indicate at least 246 million people require preventive chemotherapy against onchocerciasis(2). The prevalence of onchocerciasis in 2021 was measured as 19.6 million (95% uncertainty interval 17.8 to 21.7) an increase of 17.7% compared to 2010. In 2021, onchocerciasis was responsible for the loss of 1.26 million Disability Adjusted Life Years (95% uncertainty interval 753 000–1.90 million)(6). Key sequelae contributing to Disability Adjusted Life Years are moderate to severe skin disease and blindness(6).

Lymphatic filariasis is another filarial disease caused by three species of parasitic nematode worms that inhabit the lymphatics and subcutaneous tissues – *Wuchereria (W.) bancrofti, Brugia (B.) malayi,* and *Brugia (B.) timori*. Approximately two-thirds of those infected have subclinical disease(7). The remainder may experience acute manifestations, such as adenolymphangitis, dermatolymphangioadenitis, filarial fever, and tropical pulmonary eosinophilia, and chronic manifestations that include lymphedema and hydrocele, caused by damage to lymphatic vessels. Recurrent secondary bacterial infections of an affected extremity hasten the progression of lymphedema to its advanced stage, known as elephantiasis(8). Lymphatic filariasis disfigures and disables, often leading to stigmatisation and poverty. Hundreds of millions of dollars are lost annually due to reduced productivity of affected patients. WHO has ranked the disease as one of the world's leading causes of permanent and long-term disability(9).

Lymphatic filariasis is co-endemic with onchocerciasis in Angola, Burkina Faso, Cameroon, Chad, Congo, Cote D'Ivoire, Central African Republic, Democratic Republic of Congo, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Liberia, Mozambique, Niger, Nigeria, Tanzania, South Sudan, Sierra Leone, Senegal, and Sudan. It is also endemic in the absence of onchocerciasis in American Samoa, Comoros, Eritrea, Fiji, French Polynesia, Guyana, Haiti, India, Indonesia, Kenya, Malaysia, Madagascar, Micronesia, Myanmar, New Caledonia, Nepal, Philippines, Samoa, Papua New Guinea, Tuvalu, Zambia, and Zimbabwe(3)

Latest estimates indicate approximately 794 million people require preventive chemotherapy against lymphatic filariasis(3). The prevalence of lymphatic filariasis in 2021 was measured as 56.9 million (95% uncertainty interval 48.7 to 67.9), a decrease of 39.9% compared to 2010. In 2021, lymphatic filariasis was responsible for the loss of 1.31 million Disability Adjusted Life Years (95% uncertainty interval 770 000–2.22 million)(10). Key sequelae contributing to Disability Adjusted Life Years are lymphedema and hydrocele (10).

6.2 Current Treatment Landscape

The WHO road map for neglected tropical diseases, 2021–2030(1), has identified onchocerciasis as a disease targeted for elimination (interruption of transmission) and lymphatic filariasis for elimination as a public health problem. The targets to be reached by 2030 are:

- for onchocerciasis, to have at least 12 countries verified for elimination of transmission, to have stopped mass drug administration (MDA) in at least one focus in 34 countries, in more than 50% of the population in at least 16 countries, and in the entire endemic population in at least 12 countries.
- for lymphatic filariasis, to eliminate the need for MDA and implement post-MDA or post-validation surveillance in all 72 endemic countries and achieve validation of elimination as a public health problem in 58 of 72 endemic countries.

One of the critical actions listed to achieve these targets is to implement alternative MDA strategies or improved interventions where appropriate. Currently, these targets are not on track to be achieved.

Ivermectin, a first-generation macrocyclic lactone of the avermectin class, is included on the EML and EMLc and is presently used in MDA programs for the treatment of onchocerciasis and lymphatic filariasis in endemic regions, in accordance with the following WHO recommendations:

- In areas where onchocerciasis is endemic (in the absence of lymphatic filariasis or loiasis), the current WHO-recommended MDA regimen is ivermectin given annually (or bi-annually).
- In areas where lymphatic filariasis is endemic (in the absence of onchocerciasis or loiasis), the current WHO-recommended MDA combination regimen is annual diethylcarbamazine plus albendazole (DA) or ivermectin, diethylcarbamazine and albendazole (IDA).
- In areas where lymphatic filariasis and onchocerciasis are co-endemic (in the absence of loiasis), the current WHO-recommended MDA combination regimen is annual ivermectin and albendazole (IA).
    - Administration of diethylcarbamazine for the treatment of lymphatic filariasis can provoke a severe inflammatory reaction in patients with onchocerciasis and so is avoided in the setting of onchocerciasis.

Since ivermectin is microfilaricidal with some enduring impact on microfilariae reproduction (but not macrofilaricidal) the treatment is administered annually or biannually for approximately 15 years for onchocerciasis (the approximate lifespan of *O. volvulus* adult worms) to minimize and target elimination of transmission, and for at least 5 years in combination regimens for lymphatic filariasis.

Despite successes with ivermectin MDA for control and elimination of river blindness in some African *foci*, it is widely recognised that suboptimal response is common and alternative treatment strategies are required in many areas. The Phase 2 and 3 clinical trials for moxidectin in onchocerciasis used ivermectin as a comparator and these were the most detailed and largest clinical studies conducted in onchocerciasis in decades. In both studies, ivermectin failed to sustain skin microfilariae clearance for either 6 or 12 months (*i.e.* the two most commonly used ivermectin treatment intervals) in the majority of infected individuals. Ivermectin has also been associated with an incomplete and transient response in a substantial proportion of patients and microfilariae repopulation of the skin has been shown to occur within 3 months of treatment(11,12). This “suboptimal response” has been reported in a number of studies in patients after multiple rounds of ivermectin treatment in the Pru and lower Black Volta river basins in Ghana, the Khartoum region of Sudan and more recently in Cameroon(13–16). Suboptimal responses were also seen in a significant number of participants in the Phase 3 moxidectin study, despite no patient having previous ivermectin exposure(17). There are two clinically important consequences resulting from both unsustained and suboptimal responses to treatment: (1) the ongoing presence of microfilariae in skin and eyes is the direct cause of the pathology and morbidity of onchocerciasis, thus the cause of symptoms and deteriorating health, and; (2) the reservoir of microfilariae in the skin sustains the continued transmission of the disease and establishment of new infections. While ivermectin is the only

available treatment option for use in this disease, although not able to achieve complete suppression of microfilariae in all infected individuals, elimination in many places may not be achievable and targets will remain elusive.

In 2000, WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF). The elimination strategy has two components: (1) to stop the spread of infection (interrupting transmission), and (2) to alleviate the suffering of affected populations (controlling morbidity). Despite significant progress by the GPELF to eliminate lymphatic filariasis as a public health problem, infection rates in a variety of settings have remained above elimination targets even after many rounds of treatment(3). Progress has been particularly poor in communities co-endemic for onchocerciasis, where "gold standard" diethylcarbamazine combinations cannot be used due to safety concerns. An alternative treatment with comparable efficacy to diethylcarbamazine combinations but without the safety risks is greatly needed to ensure these areas are not left behind.

6.3 Anticipated Impact of Moxidectin

Moxidectin, a milbemycin macrocyclic lactone, is an anthelminthic medicine used in veterinary treatment of parasitic worm infections(18). Moxidectin is both microfilaricidal and embryostatic, with immediate death of the *Onchocerca* microfilariae present and delayed microfilariae repopulation following treatment. Moxidectin has a favourable pharmacokinetic profile. It can be taken without regard to food, has a simple posology, and unlike ivermectin (with a half-life of 15 hours), moxidectin's half-life is 20 – 43 days(18) with distribution in adipose tissue resulting in low and sustained systemic exposure Moxidectin 8 mg has been shown to have statistically significantly superior efficacy to ivermectin (150 µg /kg) in both Phase 2 and Phase 3 clinical trials for onchocerciasis, with a similar safety profile. A single dose of moxidectin has been shown to reduce skin microfilariae density more completely, in more people and for much longer than ivermectin. Moreover, in clinical studies the proportion of *O. volvulus* infected people achieving undetectable levels of skin microfilariae was significantly greater in those who received moxidectin than those who received ivermectin, even at 18 months post-treatment. The safety profile of moxidectin was similar to placebo in Phase 1 clinical trials and ivermectin in Phases 2 and 3.

Study NCT04410406, led by the Death to Onchocerciasis and Lymphatic Filariasis (DOLF) project team from Washington University in St Louis is evaluating the safety and efficacy of moxidectin combination treatments versus ivermectin combination treatments for Bancroftian Filariasis. This study is currently completing 36 Month follow-up visits. Data from this study indicate that a single dose of moxidectin 8 mg in combination with albendazole 400 mg (± diethylcarbamazine 6 mg/kg) was more effective than ivermectin 200 µg/kg plus albendazole 400 mg (IA) and at least as effective as ivermectin 200 µg/kg, diethylcarbamazine 6mg/kg and albendazole 400 mg (IDA) for clearance of *W. bancrofti* microfilariae, reduction of circulating filarial antigen and clearance of adult worm nests out to 24 months post-treatment. Adverse events (AE) immediately following treatment were similar in all arms. Data from this study indicate that moxidectin and albendazole (MoxA) may be at least as effective for treatment of lymphatic filariasis as IDA, offering a more effective treatment option in onchocerciasis co-endemic areas where diethylcarbamazine cannot be used for safety reasons. Month 36 data will become available before the end of 2024.

The impact of moxidectin has also been extensively studied in mathematical models. A 2015 modelling study based on Phase 2 onchocerciasis clinical trial data and using the populationbased, deterministic EPIONCHO epidemiological model, reported that both annual moxidectin and biannual ivermectin MDA would achieve similar reductions in programme duration relative to annual ivermectin treatment(19). Unlike biannual ivermectin treatment, annual moxidectin treatment would not incur a considerable increase in programmatic costs and, therefore, could generate sizeable programmatic cost savings (assuming the medicine is donated to recipient endemic countries).

An updated economic assessment of the impact of moxidectin relative to ivermectin-based strategies for onchocerciasis elimination was published in 2024 with a focus on the programmatic cost(20). Although using different parameters, the study reiterated that moxidectin-based strategies could accelerate progress toward elimination of transmission and showed that it could also reduce

programmatic delivery costs compared with ivermectin-based strategies, not including the costs of moxidectin or ivermectin tablets supplied.

The models remain sensitive to the parameters they used which brings an element of uncertainty in their results. However, a consensus statement by the Neglected Tropical Diseases Modelling Consortium (NTD-MC) tabled at the 6th meeting of the Onchocerciasis Technical Advisory Subgroup (OTS6) declared that although the available models currently predict that different durations of treatment with moxidectin or ivermectin may be needed to reach elimination, they concur that the use of moxidectin will reduce the time to elimination of onchocerciasis by ¼ to ½ that of ivermectin(21).

The results of the most recent modelling(20) also indicate that moxidectin could be a useful tool for settings where progress is lagging or settings that have not yet started treatment. This is particularly relevant for highly endemic areas where EPIONCHO-IBM projects that biannual community directed treatment with moxidectin is necessary to reach elimination of transmission within a feasible timeframe or at all. Such settings are important as these have the potential to be highly costly to Neglected Tropical Disease programmes and could potentially reintroduce infection to other controlled areas.

MDGH anticipates that moxidectin may have a similarly significant epidemiological and economic impact in lymphatic filariasis. Modelling to determine the scale of impact is currently ongoing.

Given the improved efficacy of moxidectin in onchocerciasis and lymphatic filariasis compared to ivermectin, and as demonstrated in clinical studies and via mathematical modelling, the addition of moxidectin to management of these diseases offers a more effective strategy to accelerate and achieve elimination enables cost savings for implementing countries and allows for the integration and streamlining of lymphatic filariasis and onchocerciasis elimination programmes in co-endemic settings.

7. TREATMENT DETAILS

7.1 Dosing Regimen and Duration of Treatment

The WHO currently recommends at least 12 to 15 years of annual population-based treatment (also known as mass drug administration (MDA), or preventive chemotherapy) with ivermectin to eliminate onchocerciasis, corresponding to the lifespan of the adult *O. volvulus* worm. In some areas, repeat administration every 6 months, according to the prevalence (measured by cutaneous microfilarial density) has been recommended. Moxidectin is a microfilaricide with an identical mode of action to ivermectin. It is anticipated that moxidectin will also be used annually or biannually to support countries' efforts to eliminate onchocerciasis, using a single dose of 8 mg (4 tablets of moxidectin 2 mg) to treat individuals 8 years and older and a single dose of 4 mg (2 tablets of moxidectin 2 mg) for children 4 to 7 years old.

Given the co-endemicity of onchocerciasis and lymphatic filariasis in many countries in Africa, the clinical data generated to date indicates that there will be an opportunity to use moxidectin for the treatment of lymphatic filariasis using the same dose as recommended for onchocerciasis. Additional detail on the clinical evidence in lymphatic filariasis is provided in Section 8.

7.2 Eligibility Criteria

Moxidectin was approved for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older in June 2018 by the US FDA based on a single oral dose of 8 mg (4 tablets of moxidectin 2 mg). MDGH has recently submitted a supplement to the US New Drug Application to support moxidectin's use in children 4 years and older based on an additional paediatric pharmacokinetic and safety study (further detail on this study is provided in Section 8.4). Based on these data and pharmacokinetic modelling, an oral 4 mg dose for children aged 4 to 7 years and an oral 8 mg dose for 8 years and older was proposed.

In 2024, and underpinned by the same set of data, MDGH submitted a Marketing Authorisation Application to the Ghana Food and Drugs Authority. This authorisation will initially support moxidectin use in a pilot implementation project, aiming to treat all individuals 4 years and older during MDA, as well as supporting the expected expansion into additional areas within Ghana in the future. The outcome of this application is expected by end of 2024.

There are limited data about the use of moxidectin in pregnant women. As a result, it is recommended to avoid the use of moxidectin during pregnancy. The current US FDA product information advises against breastfeeding during treatment with moxidectin and for 7 days afterwards. Available data and modelling, recently published by Wood et al in 2024(22) has been provided to the Ghana Food and Drugs Authority to underpin decisions on the public health use of moxidectin during breast-feeding. This may result in guidance similar to that for ivermectin in such treatment programmes.

Patients who are infected with *Loa loa* may develop a serious or even fatal encephalopathy following treatment with moxidectin. Data on moxidectin in patients co-infected with *Loa loa* is limited (23). Therefore, it is recommended that individuals who warrant treatment with moxidectin and have had significant exposure to *Loa loa* -endemic areas undergo diagnostic screening for loiasis prior to treatment.

7.3 Administration

Moxidectin administration does not require any specific skills and is expected to be dispensed to individuals by community drug distribution volunteers during MDA campaigns as is being done with ivermectin. However, unlike ivermectin, dosage is determined by age (not by height) with a 4 mg dose for children aged 4 to 7 years and an 8 mg dose for 8 years and older. For areas where age determination in children is difficult, a height approximation could be developed. Moxidectin can be administered with or without food.

8. REVIEW OF EVIDENCE FOR BENEFITS AND HARMS

8.1 Overview

All available data on moxidectin for treatment of onchocerciasis and lymphatic filariasis indicate superior efficacy and similar safety to ivermectin.

A systematic review commissioned by the WHO NTD department was conducted in 2022 by Dr. Dziedzom K. de Souza (Noguchi Memorial Institute for Medical Research, University of Ghana, Accra, Ghana) to assess the safety and efficacy of using moxidectin to treat entire populations in onchocerciasis endemic areas. This report was presented and discussed at the sixth meeting of the Onchocerciasis Technical Advisory Subgroup of the WHO(24). Sally Kinrade from MDGH was one of the individuals who provided support in the creation of this report. The report is the most recent systematic literature review conducted on moxidectin treatment for onchocerciasis. Publications for inclusion were identified by searching Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, EMBASE, LILACS and WHOLIS, Web of Science and RePORTER databases using the search terms ((moxidectin) AND ((onchocerciasis OR river blindness OR *Onchocerca volvulus*) OR (*Loa loa* OR loiasis) OR (lymphatic filariasis OR elephantiasis river blindness OR *Wuchereria bancrofti*) OR (*Trichuris trichiura*) OR (*Ascaris lumbricoides*) OR (*Schistosoma haematobium*) OR (*Schistosoma mansoni*) OR (Hookworm OR *Necator americanus*) OR (*Strongyloides stercoralis*)). All published studies in humans, irrespective of geographical location, language, period/year of study, gender and age were included in the analysis. The report concluded that the evidence supports the use of moxidectin for the control of onchocerciasis in endemic populations. The full content of the report is not reiterated here. Instead references to key information will be made in the subsequent sections.

In August 2024, MDGH conducted a search of the PubMed database using the same search terms employed in the 2022 systematic review(24) to identify any additional studies that have since been published which could help strengthen the evidence and address other questions, including the efficacy of moxidectin for treatment of lymphatic filariasis. Six additional publications were identified and are discussed in Section 8.2.

Other moxidectin studies are still ongoing or have recently reached completion with results not yet published. These studies are discussed in Sections 8.4 and 8.5. When available, data from these studies will add to the evidence for benefits and harms.

8.2 Evidence of Efficacy

The 2022 systematic review assessed the evidence for the efficacy and safety of moxidectin for the control and elimination of onchocerciasis(24). For review of efficacy, multiple databases were searched for randomized controlled trials (RCTs) that investigated the impact of single-dose treatments with ivermectin and moxidectin on onchocerciasis and other helminth infections. The certainty of the evidence, for the outcomes of interest, was assessed only for the included RCTs, using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. Full detail on search methodology, including databases interrogated, search terms, and filters are provided in the review report (24).

Two RCTs (Awadzi et al(25) and Opoku et al(26)) conducted in onchocerciasis-infected adults and adolescents met the criteria for inclusion in the systematic review. In these studies, the efficacy of moxidectin 8 mg was statistically significantly superior compared to 150 µg/kg ivermectin at 6 and 12 months post-treatment. Pooled analysis from the two RCTs showed increased odds of skin microfilariae clearance post-treatment in the moxidectin group compared to the ivermectin group (odds ratio 2.81; 95% confidence interval 0.95–4.68; medium quality of evidence).

Given that treatment with moxidectin will be given to populations coinfected with other neglected tropical diseases, a secondary objective of this systematic review was to assess the efficacy of moxidectin for the control and elimination of other filarial and helminth infections. The authors identified no added impact of moxidectin for the treatment and control of *S. stercoralis*, *T. trichiura*, *S. haematobium* and *S. mansoni* compared with ivermectin. The available evidence showed that

outcomes in these diseases would be similar to those with ivermectin. As the review predates the lymphatic filariasis data, there was insufficient evidence at the time of the review to determine whether moxidectin could be used for annual MDA to eliminate lymphatic filariasis in implementation units co-endemic for onchocerciasis(24).

In August 2024, MDGH conducted a search of the PubMed database using the same search terms employed in the aforementioned systematic review(24). No new publications of relevance to the assessment of efficacy of moxidectin for the control and elimination of onchocerciasis were identified. However, an additional three publications were identified as contributing to the evidence on the efficacy of moxidectin in other filarial and helminth infections:

- Wafeu et al(23) reported efficacy findings of a double-blind, randomized, ivermectin-controlled trial comparing a 2 mg moxidectin dose and the standard 150 µg/kg ivermectin dose for onchocerciasis in individuals with low *Loa (L.) loa* microfilarial densities (NCT04049851). The study was conducted in Cameroon and enrolled 72 adult men with *L. loa* microfilarial density between 5 and 1000 microfilariae/mL. A key outcome was *Loa loa* microfilarial density reduction rate during the first month after treatment. Data showed that median microfilarial density reduction rates were significantly higher after ivermectin than moxidectin at Day 3 (70.2% vs 48.5%), Day 7 (76.4% vs 50.0%), and Day 30 (79.8% vs 48.1%). The authors concluded that further studies with higher doses of moxidectin (up to the standard dose of 8 mg used for treatment of onchocerciasis) and in patients with higher *L.loa* microfilarial densities are warranted.
- Sprecher et al(27) reported efficacy findings from a community-based, randomized, placebo-controlled, parallel-group superiority trial of moxidectin 8 mg plus albendazole 400 mg and ivermectin 200 µg/kg plus albendazole 400 mg combination therapy compared to albendazole monotherapy in adolescents and adults infected with *Trichuris trichiura* in Côte D'Ivoire (NCT04726969). The primary outcome was proportion cured, ie, cure rate, assessed at 2-3 weeks post-treatment. For the 210 participants with primary outcome data, the authors observed cure rates of 15.3% in the moxidectin-albendazole arm and 22.5% in the ivermectin-albendazole arm, which did not differ significantly from the cure rate of 13.4% in the albendazole arm (differences: 1.8%- points [95% confidence interval -10.1 to 13.6] and 9.1%-points [-3.9 to 21.8], respectively). The authors concluded that all therapies showed similar low efficacy in treating trichuriasis in Côte d'Ivoire.
- Sprecher et al(28) reported efficacy findings from a randomised, double-blind, parallel-group, non-inferiority, Phase 2b/3 trial of single oral doses of either moxidectin (8 mg) or ivermectin (200 µg/kg bodyweight) for *Strongyloides stercoralis* in adults in Laos and Cambodia (NCT04056325). 726 participants were enrolled and randomly assigned to moxidectin (n=363) or ivermectin (n=363). The primary endpoint was cure rate assessed at 14–21 days after treatment. For the participants with primary outcome data, the authors observed a cure rate of 93·6% (95% confidence interval 90·5 to 96·0; 324 of 346 participants) in the moxidectin group and 95·7% (93·0 to 97·6; 335 of 350 participants) in the ivermectin group, resulting in a between-group difference of –2·1 percentage points (95% confidence interval –5·5 to 1·3). The authors concluded that moxidectin was non-inferior to ivermectin in terms of efficacy in the treatment of strongyloidiasis.

8.3 Evidence of Safety

In addition to the US FDA's peer review of all non-clinical and clinical safety data, to assess safety of moxidectin for the control and elimination of onchocerciasis, the 2022 systematic review(24) considered data from RCTs and pharmacokinetic studies that investigated the impact of single-dose treatments with ivermectin and moxidectin. The certainty of the evidence, for the outcomes of interest, was assessed only for the included RCTs, using the GRADE approach.

Pooled analysis from the two RCTs identified for inclusion showed that there was no significant difference in the occurrence of AEs among community members post-treatment between the moxidectin and ivermectin groups (odds ratio 0.43; 95%; confidence interval -1.64 to 2.5; medium

quality of evidence). The absolute risk indicates 37 fewer per 1000 persons experiencing an AE after treatment with moxidectin compared with ivermectin. The report concluded that the safety profile was similar between moxidectin and ivermectin, with no significant differences in safety identified with treatment of onchocerciasis-infected individuals. A full description of AE profiles of each of the studies included in the systematic review are provided in the review report (24).

The authors noted that there was insufficient data available to evaluate whether moxidectin is safe to use in implementation areas co-endemic for onchocerciasis and lymphatic filariasis or loiasis. They note that the results of ongoing clinical trials in Côte D'Ivoire and Cameroon should help address these questions when the data become available. Since this systematic review was published, pharmacokinetic and safety data from these two studies have been published.

Key findings are as follows:

- Chonker et al(29) reported the findings from a study on the pharmacokinetics and drug interactions of a combination of moxidectin 8 mg plus albendazole 400 mg with or without diethylcarbamazine 6 mg/kg compared to ivermectin 0.2 mg/kg plus albendazole 400 mg with or without diethylcarbamazine 6 mg/kg (NCT04410406). Fifty-eight of 164 study participants (53 men and 5 women) were included with ages ranging from 18 to 63 years (mean = 37). The authors concluded that the addition of moxidectin to albendazole alone or albendazole plus diethylcarbamazine for lymphatic filariasis therapy did not alter the drug exposure of co-administered drugs compared to ivermectin combinations.
- In a second publication from study NCT04410406, Bjerum et al(30) reported on the safety and tolerability of moxidectin and ivermectin combination treatments for lymphatic filariasis. In this study, all participants were closely monitored for 7 days after treatment. One hundred and sixty-four individuals were treated and monitored for treatment-emergent adverse events (TEAE). Eighty-seven participants (53%) experienced one or more mild (Grade 1) or moderate (Grade 2) TEAEs. Four participants had transient Grade 3 haematuria after treatment (3 after IDA and 1 after IA). There were no serious adverse events (SAE). There were no significant differences in frequency or types of TEAE between treatment groups (IA = 22/41 (53%), MoxA = 24/40 (60%), IDA = 18/41 (44%), MoxDA = 15/42 (36%), p = 0.530). Fifty-nine participants (36%) had multiple TEAEs, and 8.5% had a one or more grade 2 (moderate) TEAEs. Grade 2 TEAEs were more frequent after triple drug treatments (IDA, 14.6%; MoxDA, 9.5%) than after two-drug treatments (IA, 7.3%; MoxA, 2.5%). There was no difference in TEAEs based on baseline microfilariae counts (odds ratio 0.69 (0.33, 1.43), p-value 0.319). The authors concluded that all treatment regimens were well tolerated and no difference in safety parameters between regimens that contained ivermectin or moxidectin were observed.
- Wafeu et al.(23) reported safety findings of a double-blind, randomized, ivermectin-controlled trial comparing a 2 mg moxidectin dose and the standard 150 µg/kg ivermectin dose in individuals with low *Loa loa* microfilarial density (NCT04049851). The study was conducted in Cameroon and enrolled 72 adult men with *Loa loa* microfilarial densities between 5 and 1000 microfilariae/mL. The safety outcome was the occurrence of AEs during the first month of treatment. No serious or severe AEs occurred among the 36 moxidectin or the 36 ivermectin-treated individuals. Forty-nine AEs occurred in the moxidectin arm versus 59 AEs in the ivermectin arm. Grade 2 AE incidence was higher among ivermectin than moxidectin-treated participants (38.5% and 14.3%, respectively, $P = 0.043$). The authors concluded that a single 2 mg moxidectin dose is as safe as 150µg/kg ivermectin in patients with low *Loa loa* microfilariae density and that further studies with higher moxidectin doses and in patients with higher microfilarial densities are warranted.

In August 2024, MDGH conducted a search of the PubMed database using the same search terms employed in the aforementioned systematic review(24) to identify any additional studies that have since been published that add to the evidence for safety of moxidectin. In addition to the three publications described above(23,29,30), an additional three publications of relevance were identified:

- Kanza et al(31) analysed data from the Phase 3 RCT comparing the efficacy and safety of a single oral dose of 8 mg moxidectin and 150 µg/kg ivermectin in *O. volvulus* infected individuals (NCT00790998; Original study publication by Opoku et al(26)). In this publication, Kanza et al report the number of microfilariae in the anterior chamber (mfAC) of the eye(s) before treatment, 4 days and 1, 6, 12 and 18 months after treatment and their relationship to pre- and post-treatment skin microfilariae density (SmfD) as well as the ocular AEs observed within 6 months post-treatment. Results from this analysis indicated that moxidectin and ivermectin had the same effect on mfAC levels. These increased from pre-treatment to Day 4 and Month 1 in 20% and 16% of participants, respectively. Six and 12 months post-treatment, mfAC were detected in approximately 5% and 3% of participants respectively. Ocular Mazzotti reactions occurred in 12.4% of moxidectin and 10.2% of ivermectin-treated participants without differences in type or severity. The risk for ≥ 1 ocular Mazzotti reaction increased for women (odds ratio 1.537, 95% confidence interval 1.096–2.157) and with mfAC levels pre- and 4 days post-treatment (odds ratio 0: > 10 mfAC 2.704, 95% confidence interval 1.27–5.749 and 1.619, 95% confidence interval 0.80–3.280, respectively).
- Sprecher et al(27) reported safety findings from a community-based, randomized, placebo-controlled, parallel-group superiority trial of moxidectin 8 mg plus albendazole 400 mg and ivermectin 200 µg/kg plus albendazole 400 mg combination therapy compared to albendazole monotherapy in adolescents and adults infected with *Trichuris(T.) trichiura* in Côte D'Ivoire (NCT04726969). Safety endpoints were assessed pre-treatment and at 3- and 24-hours post-treatment. In total, 102 of 255 participants (40.0%) experienced an AE, which were evenly distributed among the 3 treatment arms: 37 of 86 (43.0%) who received ivermectin-albendazole, 34 of 85 (40.0%) who received moxidectin-albendazole, and 31 of 84 (36.9%) who received albendazole. The most common AEs were abdominal pain (range across arms: 11.9%-20.9%), headache (4.7%- 14.3%), and itching (5.8%-13.1%), which were predominantly mild and transient.
- Sprecher et al(28) reported safety findings from a randomised, double-blind, parallel-group, non-inferiority, Phase 2b/3 trial of single oral doses of either moxidectin (8 mg) or ivermectin (200 µg/kg bodyweight) for *Strongyloides stercoralis* in adults in Laos and Cambodia (NCT04056325). 726 participants were enrolled and randomly assigned to moxidectin (n=363) or ivermectin (n=363). Safety endpoints were assessed before treatment, and at 2–3 h, 24 h, and 14–21 days after treatment. 153 (21%) of 726 participants had an AE after treatment, evenly distributed among the two treatment groups in both countries: 74 (20%) of 363 participants who received moxidectin and 79 (22%) of 363 participants who received ivermectin had an AE. The most common AEs were abdominal pain (32 [9%] of 363 with moxidectin *vs* 34 [9%] of 363 with ivermectin) and headache (25 [7%] *vs* 30 [8%]), which were predominantly mild and transient.

8.4 Completed Studies with Unpublished Results

Completed MDGH-sponsored or MDGH-supported clinical trials where results were not journal-published at the time of this submission and hence not considered in the systematic review of published literature described in sections 8.2 and 8.3 are summarised in Table 4 and described below.

Table 4: Overview of Completed (Unpublished) MDGH Sponsored or Supported Clinical Trials with Moxidectin for Onchocerciasis and Lymphatic Filariasis

Protocol	Study Design	Subjects	Moxidectin Dose
Onchocerciasis			
MDGH-MOX-1006 An open-label study of the pharmacokinetics and safety of a single dose of moxidectin per	Phase I, open-label, pharmacokinetics and safety in adolescents and	36 adolescents and children 4 to 17 years	Tablets (2mg): 12 to 17 years (n=9): 8 mg

Protocol	Study Design	Subjects	Moxidectin Dose
oral 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. Ghana ClinicalTrials.gov NCT03962062 PACTR201907565746388 IND 126876	children 4 to 17 years		8 to 11 years (n = 9): 8 mg 8 to 11 years (n = 9): 6 mg 4 to 7 years (n = 9): 4 mg
Lymphatic filariasis			
NCT04410406 A randomized, open-label, masked-observer superiority trial of moxidectin combination regimens for treatment of *W. bancrofti* infection in adults ClinicalTrials.gov NCT04410406	Phase II, randomized, open-label, masked-observer superiority trial	164 adults 18 to 70 years with *W. bancrofti* infection	8 mg (n = 82)

Study MDGH-MOX-1006 (Clinicaltrials.gov identifier: NCT03962062)

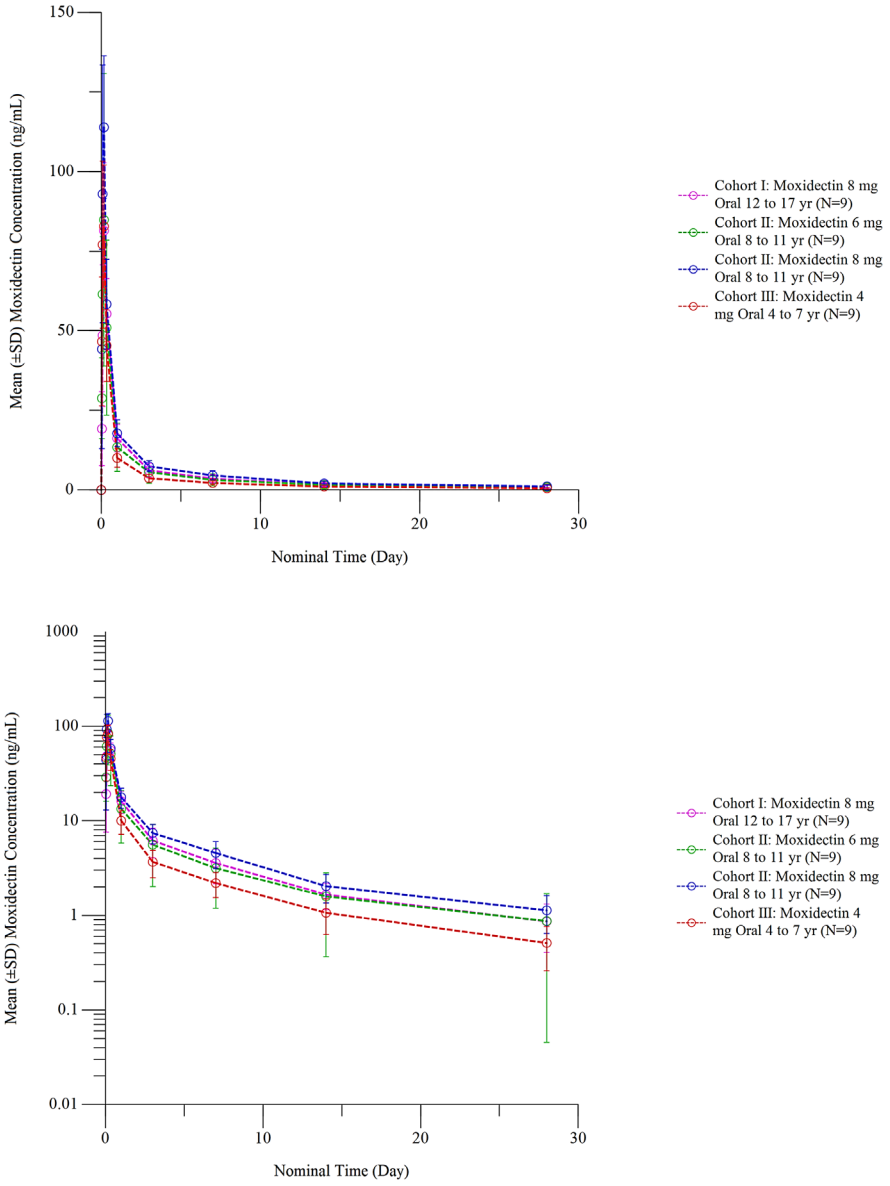
The pharmacokinetics and safety of moxidectin has been evaluated in children and adolescents in study MDGH-MOX-1006. Thirty-six Ghanaian pediatric participants aged 4 to 17 years with or at risk of onchocerciasis were enrolled in 3 cohorts and a single dose of moxidectin administered: 8 mg (Cohort I; 12 to 17 years), 6 or 8 mg (Cohort II; 8 to 11 years), or 4 mg (Cohort III; 4 to 7 years). The study used an adaptive approach that iteratively analyzed moxidectin pharmacokinetics as observed data from each Cohort became available. Per the study protocol, participants in Cohort II were to receive a single dose of 8 mg. The selection of lower doses (6 mg in Cohort II and 4 mg in Cohort III) was based on simulations from an updated interim population pharmacokinetic model that analyzed available data from adults, adolescents and a first group of children (8 to 11 years), as well as an evaluation of safety. Pre-specified criteria in the protocol required that in the event that 3 or more participants in Cohort II or Cohort III had moxidectin exposure results outside the 10^{th} to 90^{th} percentile area under the concentration: time curve from Day 0 to Day 28 predicted by the original model in adults, an alternative dose be selected and 9 new participants in that age cohort be enrolled and treated at the new dose. Based on those criteria, 9 additional participants were enrolled to Cohort II and received a dose of 6 mg moxidectin.

Moxidectin was well tolerated in study MDGH-MOX-1006, with no TEAE considered related to study drug, no SAEs, and no TEAEs leading to study withdrawal or resulting in death. The most frequently reported TEAE overall was malaria, followed by upper respiratory tract infection, abdominal pain, diarrhea and conjunctivitis. The majority of TEAEs reported were Grade 1 (mild) in severity, with the remainder assessed as Grade 2 (moderate) and Grade 3 (severe). There were no Grade 4 (life-threatening) TEAEs reported. Grade 2 (moderate) severity TEAEs included malaria, upper respiratory tract infection, and false positive investigation result. Grade 3 (severe) TEAEs included hookworm infection and anemia in the same subject. There were no clinically significant

trends in changes in safety laboratory parameters, vital signs or physical examination findings observed and no notable trends or differences in concomitant medication usage between cohorts.[1]

Moxidectin was quantifiable in all subjects up to Day 28. At Week 12, moxidectin was quantifiable in 50% of the subjects in Cohort I and II, and none of the subjects in Cohort III. Mean plasma moxidectin concentration-time profiles on both linear-linear and log-linear scales for all available data are shown for the first 28 days in Figure 1 and truncated to the first 24 hours after dosing in Figure 2. Mean concentrations were not calculated and depicted if > 50% of the subjects had concentrations below the limit of quantitation or missing concentrations. Dose normalized mean plasma moxidectin concentration-time profiles on log-linear scale for all available data are shown in Figure 3.

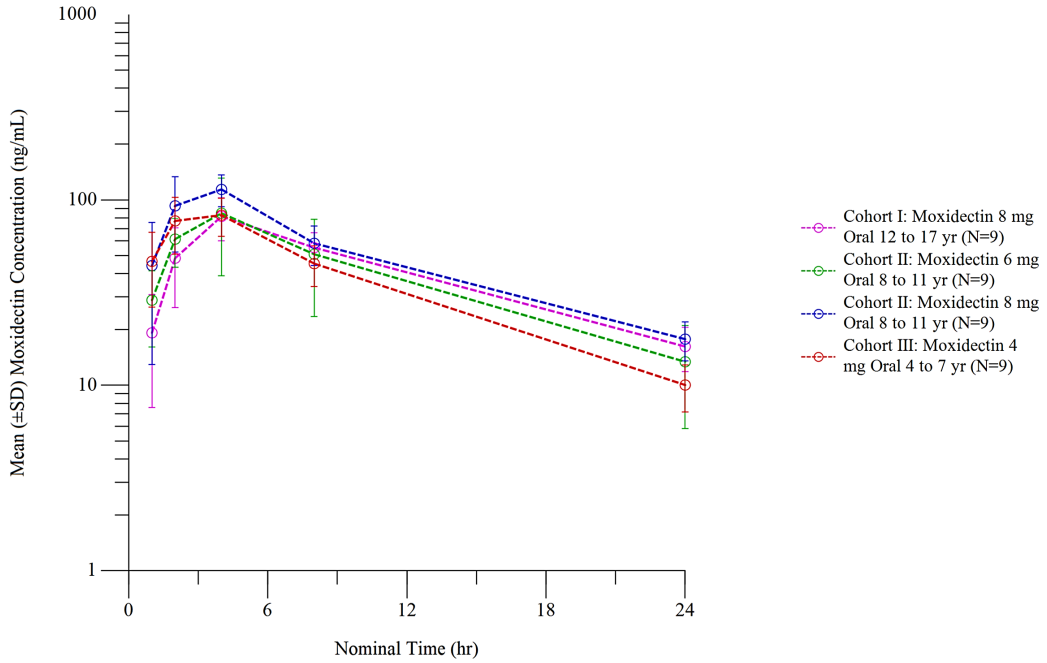
Figure 1: Mean (±SD) Plasma Moxidectin Concentrations over Time [Upper Panel: Linear Scale and Lower Panel: Log-Linear Scale] (PK Population)[2]



SD: Standard Deviation

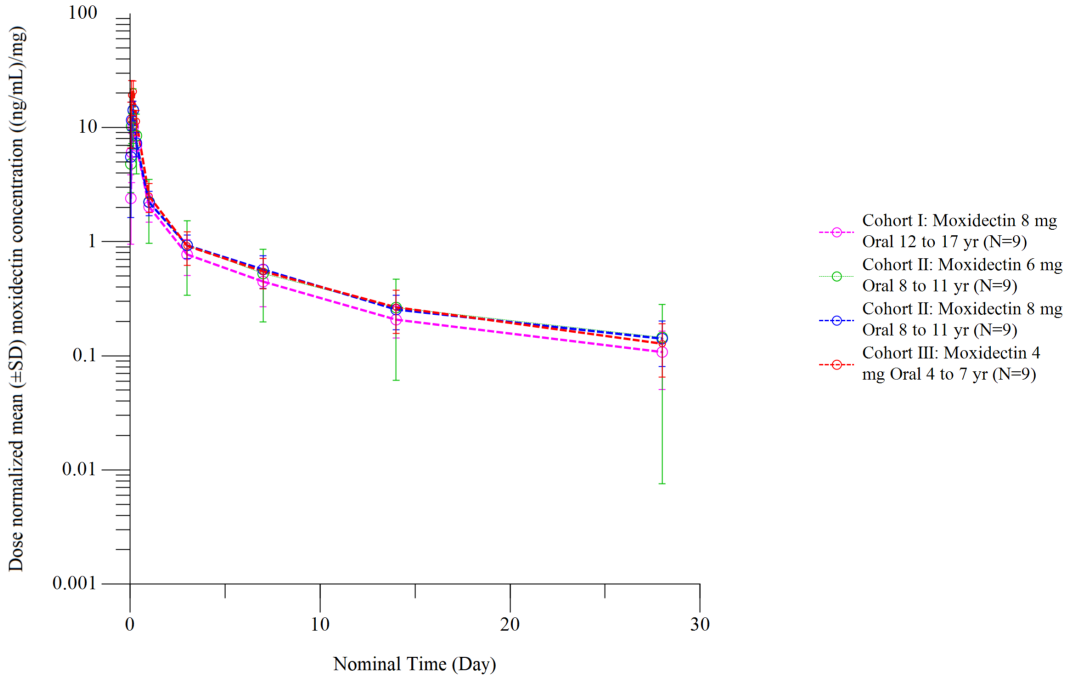
[1]Medicines Development for Global Health, unpublished data
[2] Medicines Development for Global Health, unpublished data

Figure 2: Mean (±SD) Plasma Moxidectin Concentrations over Time - Day 1 [Log-Linear Scale] (PK Population)[3]



SD: Standard Deviation

Figure 3: Dose Normalized Mean (±SD) Plasma Moxidectin Concentrations over Time [Log-Linear Scale] (PK Population)[4]



SD: Standard Deviation

[3] Medicines Development for Global Health, unpublished data
[4] Medicines Development for Global Health, unpublished data

Data from study MDGH-MOX-1006 indicate that doses of moxidectin of 6 mg in children aged 8 to 11 years and 4 mg in children aged 4 to 7 years provide comparable exposures to those achieved in adolescents aged 12 to 17 years and adults with the approved dose of 8 mg moxidectin. As anticipated, the observed Cmax and AUC0-inf at these doses in children fall well below those achieved at the highest dose of 36 mg moxidectin tested in clinical studies in adults, a dose that was shown to be well-tolerated.A simpler dosing regimen to support ease of operationalisation in field treatment programmes has been proposed and was investigated using the moxidectin population pharmacokinetic model and relevant weight for age growth charts. Simulations identified that an age-based regimen consisting of a 4 mg dose for children 4 to <8 years and an 8 mg dose for children and adolescents ≥8 to 17 years provides a pharmacokinetically-optimized and simplified age-based alternative to three different doses across the age range from 4 years to adults. The safety of this dose regimen is currently being further examined in a clinical study assessing the safety of single dose moxidectin compared to single dose ivermectin in participants 4 years and older being conducted in the Democratic Republic of Congo and Côte d'Ivoire.

Study NCT04410406

Study NCT04410406 is a clinical trial led by the Death to Onchocerciasis and Lymphatic Filariasis (DOLF) project team from Washington University in St Louis being conducted in Côte d'Ivoire to assess the safety and efficacy of moxidectin combination treatments versus ivermectin combination treatments for Bancroftian Filariasis.

This trial is a single-site, randomized, open-label, masked-observer superiority trial with four treatment arms: ivermectin and albendazole (IA), moxidectin and albendazole (MoxA), ivermectin, diethylcarbamazine and albendazole (IDA), and moxidectin, diethylcarbamazine, and albendazole (MoxDA). All participants received a single dose of treatment, except for those in the IA arm who received a second dose of IA at 12 months after the initial dose (as is standard of care). The primary endpoint was the proportion of participants achieving complete clearance of microfilaremia at 12 months (IA vs. MoxA comparison) or 24 months (IDA vs. MoxDA comparison). Secondary endpoints include decrease in circulating filarial antigen (CFA) (based on semiquantitative reading of filarial test strips) and clearance of adult worm nests in men as assessed by scrotal ultrasound. This study enrolled 164 participants. Participants were followed up for 36 months following treatment. Enrollment for this study commenced in August 2020 and the study participant visits concluded in September 2024. Safety results from this study have been published(29,30) and were outlined in Section 8.3

Efficacy results remain unpublished at the time of submission of this application. The study efficacy manuscript is expected to be published by early 2025. However, preliminary results were presented at the 2022 and 2023 annual meetings of the American Society for Tropical Medicine and Hygiene (ASTMH).

- 12-month data were presented in 2022 when 87% of participants had been reevaluated at 12 months post-treatment. Complete microfilariae clearance was achieved and sustained through 12 months in 100% of MoxA (15/15) and MoxDA (20/20) participants, compared with 19/22 (86%) IDA and 6/21 (29%) IA (control) participants (p<0.001). Semiquantitative filariasis test strip scores, (related to adult worm burdens) decreased in 8 (36%) IDA and 9 (45%) MoxDA participants, compared to 2 (13%) MoxA and 1 (5%) IA participants (p=0.008). Among those with scrotal worm nests detectable by ultrasound at baseline, 11/12 (92%) IA participants had detectable worm nests at 12 months vs 3/10 (30%) after IDA, 3/8 (38%) after MoxA, and 4/10 (40%) after MoxDA (p = 0.01). These data show that MoxA is superior to IA and comparable to IDA and MoxDA for sustained clearance of microfilariae through 12 months post-treatment. Greater reduction in filariasis test strip scores after treatments that included diethylcarbamazine is consistent with that drug's known macrofilaricidal effect. IDA, MoxDA, and MoxA all appear superior to IA for inactivating adult worm nests(32).
- 24-month data were presented in 2023 when roughly half of 24 month efficacy data had been collected and analysed. At 24 months 9 of 19 (47%) participants in the IA arm (after two

annual doses) had undetectable microfilariae compared to 13 of 14 (93%) participants in the single dose MoxA arm (p=0.006). There was no difference in microfilariae clearance between single dose IDA and MoxDA (81% vs 88% respectively, p=0.576). Adult worm nests were cleared in 2 of 11 (18%) men after IA and 7/8 (88%) of men after MoxA. Sixty percent of men (3 of 5) cleared their worm nests after IDA compared to 100% (9/9) after MoxDA (p=0.171). There was no difference in reduction of CFA between IA and MoxA (11% vs 36%, p=0.08) at 24 months, however more people in MoxDA compared to IDA (53% vs 19%, p=0.041) had reduction in CFA. These preliminary data strongly suggest that MoxA is superior to IA and comparable to the diethylcarbamazine-containing regimens (which cannot be used in most of Africa) for clearance of *W. bancrofti* microfilaremia and inactivation of adult worm nests at 24 months(33).

8.5 Ongoing Studies

Table 5 shows ongoing clinical trials whose results, when available, can help strengthen the evidence.

Table 5: Overview of Ongoing MDGH-Sponsored Clinical Trials with Moxidectin

Protocol	Study Design & Subjects	Dose	Status
Onchocerciasis			
MDGH-MOX-3001 A randomized, double blind, parallel trial in the Democratic Republic of Congo (DRC) comparing the safety and efficacy of annual or biannual doses of moxidectin or ivermectin for treatment of onchocerciasis. Democratic Republic of Congo ClinicalTrials.gov NCT03876262 PACTR202004639229710 IND 126876	Phase IIIb, randomized, double-blind, parallel 3 to 3 to 1 to 1 treatment assignment (bMOX vs aMOX vs bIVM vs aIVM) 323 subjects Adolescents and adults 12 years and over with onchocerciasis	MOX 8 mg or IVM 150 µg/kg	Completion (last participant last visit at Month 36) expected in July 2026 Primary analysis of the study after all participants reached Month 12 visits, results available in Dec 2024 and clinical study report in Q1 2025.
MDGH-MOX-3002 A randomized, double blind, parallel-group clinical trial to evaluate the safety of moxidectin compared with ivermectin in individuals living in onchocerciasis endemic areas and in individuals living in onchocerciasis endemic areas with high levels of lymphatic filariasis co-endemicity receiving concomitant treatment with albendazole Democratic Republic of Congo and Cote D'Ivoire ClinicalTrials.gov NCT04311671 PACTR202003567524647	Phase IIIb, randomized, double-blind, parallel 4 to 1 treatment assignment 12 997 subjects randomised and dosed Children (4 years and over), adolescents and adults living in an onchocerciasis endemic area	Single dose MOX 8 mg or IVM 150 µg/kg	Completed; results available in March 2025.
Scabies			

Protocol	Study Design & Subjects	Dose	Status
MDGH-MOX-2002 A placebo-controlled, double-blind, randomized, dose-ranging, efficacy and safety study of orally administered moxidectin in adults with scabies Dominican Republic, ElSalvador, Honduras, Puerto Rico, United States ClinicalTrials.gov NCT05875441 IND 138487	Phase II, placebo controlled, randomized, double-blind 200 adults aged 18 years and older diagnosed with scabies	Single dose MOX 8 mg or MOX 16 mg or MOX 32 mg	Recruitment complete; results available early 2025

MOX: moxidectin: IVM: ivermectin b:biannual; a:annual

8.6 Conclusion

Despite the success of ivermectin in controlling river blindness in some regions, alternative treatments have been sought by WHO for many years(34). Clinical trials of moxidectin, comparing it with ivermectin, have shown that ivermectin often fails to maintain skin microfilariae clearance which is reflected in continued disease transmission in many regions. Additionally, the WHO's Global Programme to Eliminate Lymphatic Filariasis has faced challenges with persistent transmission, particularly in areas co-endemic with onchocerciasis where diethylcarbamazine cannot be used due to safety concerns. The following is a summary of the evidence available to support the use of moxidectin as an alternative to ivermectin for treatment of filarial diseases onchocerciasis and lymphatic filariasis.

Evidence on moxidectin for treatment of onchocerciasis in areas not co-endemic for *Loa Loa*

Review of all available evidence supports the use of moxidectin for the control of onchocerciasis in endemic populations where *Loa loa* is not co-endemic. Improved extent and durability of control of onchocerciasis skin microfilariae, as evidenced by significantly higher proportions of individuals with undetectable skin microfilariae at 1, 6 and 12 months after a single dose of moxidectin compared with ivermectin is anticipated to greatly reduce the transmission of *O. volvulus*, resulting in a positive impact on potential for achieving and times to reaching disease elimination. An ongoing study of annual or biannual repeat treatment with moxidectin or ivermectin (MDGH-MOX-3001) will provide additional evidence to inform optimal dosing frequency of both medicines. Data from the first 12 months of treatment and follow-up of all participants will be available in early 2025. The safety profile is similar between moxidectin and ivermectin, with no significant differences in safety with treatment of onchocerciasis-infected individuals identified.

Evidence on moxidectin for treatment of onchocerciasis in areas co-endemic for lymphatic filariasis

Results of a randomised open label clinical trial has shown that moxidectin combination treatments have the same TEAE profile as the equivalent ivermectin combinations that are widely used in MDA programs to eliminate lymphatic filariasis, including in areas where onchocerciasis is co-endemic(30). Additional data from an ongoing large safety study of moxidectin in people aged 4 years and older living in areas co-endemic for onchocerciasis and lymphatic filariasis receiving concomitant treatment with albendazole (MDGH-MOX-3002) will provide additional evidence on safety of treatment in this population, available in early 2025.

Evidence on moxidectin for treatment of onchocerciasis in areas co-endemic for *Loa loa*

Available data on the safety of moxidectin in individuals with loiasis is limited to a single study which used a 2 mg dose of moxidectin in people with low microfilarial density(23). Although a single 2 mg moxidectin dose appears to be as well tolerated as 150 µg/kg ivermectin in patients with low

Loa loa microfilariae density, further studies are needed to determine whether the safety profile for moxidectin 8 mg indicates it could be used for the treatment of onchocerciasis or lymphatic filariasis in areas where loiasis is co-endemic.

Evidence on moxidectin for treatment of lymphatic filariasis in areas co-endemic for onchocerciasis

Preliminary data from a recently completed study (study NCT04410406) indicates that moxidectin in combination with albendazole may be more effective at clearing *W. bancrofti* microfilaremia than ivermectin plus albendazole, the current standard of care in areas co-endemic for onchocerciasis, and with a similar safety profile. Efficacy results of this study are anticipated to be published in late 2024.

Evidence on moxidectin for treatment of other helminth infections in areas co-endemic for onchocerciasis

Given that treatment with moxidectin will be given to populations coinfected with other neglected tropical diseases, the evidence on the added impact of moxidectin for the treatment and control of *S. stercoralis*, *T. trichiura*, *S. haematobium* and *S. mansoni* was considered. The available evidence shows that treatment outcomes in these diseases would be similar to those for ivermectin.

9. SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES

The WHO guideline development group is currently reviewing the available evidence to support the development of guidelines on moxidectin for the treatment of onchocerciasis and lymphatic filariasis. These guidelines are expected to be published in early 2026.

An overview of current treatment guidelines for onchocerciasis and lymphatic filariasis is provided in sections 9.1 and 9.2, respectively.

9.1 Onchocerciasis

There is currently no WHO treatment guideline published for onchocerciasis.

The WHO webpage on onchocerciasis recommends treating onchocerciasis with ivermectin at least once yearly for 12 to 15 years(5). This is reiterated in the WHO Onchocerciasis Guidelines for stopping MDA and verifying elimination of human onchocerciasis(35) where the current intervention strategy for onchocerciasis is based on MDA with ivermectin. This treatment regimen may need to be adjusted in regions where onchocerciasis is co-endemic with loiasis, another filarial disease caused by the *Loa loa* parasite, as treating individuals with high levels of *Loa loa* may cause SAEs(5).

Moxidectin is not yet included in national treatment guidelines of countries in which onchocerciasis is endemic.

9.2 Lymphatic filariasis

The WHO-recommended preventive chemotherapy strategy for lymphatic filariasis elimination is MDA. The MDA regimen recommended is dependent on the co-endemicity of lymphatic filariasis with other filarial diseases, as detailed in the treatment guideline and as extracted in Table 6.

In summary, WHO treatment guidelines for lymphatic filariasis recommend the following regimens(9):

- albendazole (400 mg) alone twice per year for areas co-endemic with loiasis;
- ivermectin (200 µg/kg) with albendazole (400 mg) in countries with onchocerciasis;
- diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in countries without onchocerciasis; and
- ivermectin (200 µg /kg) together with diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in countries without onchocerciasis and where other programmatic conditions are met.

Table 6: WHO Recommendations on Alternative MDA Regimens to Eliminate Lymphatic Filariasis(9)

In countries using DA to eliminate lymphatic filariasis (endemic for lymphatic filariasis but without either onchocerciasis or loiasis)		
Recommendation	**Strength of recommendation**	**Quality of evidence**
WHO recommends annual IDA rather than annual DA in the following special settings: • for IUs that have not started or have fewer than four effective rounds of DA; • for IUs that have not met the epidemiological thresholds in sentinel and spot-check site surveys or in transmission assessment surveys despite meeting drug coverage targets; and	Conditional recommendation	Low

• for communities where post-MDA or post-validation surveillance identified infection suggesting local transmission.		
WHO recommends annual DA rather than biannual DA.	Conditional recommendation	Low
In countries using IA to eliminate lymphatic filariasis (endemic for lymphatic filariasis and either having onchocerciasis or being co-endemic for loiasis)		
Recommendation	**Strength of recommendation**	**Quality of evidence**
(Onchocerciasis endemic in any part of the country) WHO recommends annual IA rather than annual IDA.	Conditional recommendation	Low
(Onchocerciasis endemic in any part of the country) WHO recommends annual IA rather than biannual IA, except in areas where biannual distribution of ivermectin is already being delivered for onchocerciasis.	Conditional recommendation	Very low
WHO recommends biannual albendazole rather than annual albendazole in IUs where LF is co-endemic with loiasis and ivermectin has not already been distributed for either onchocerciasis or LF.	Conditional recommendation	Very low

DA: diethylcarbamazine and albendazole; IA: ivermectin and albendazole; IDA: Ivermectin, diethylcarbamazine and albendazole; IU: implementation unit

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST EFFECTIVENESS

MDGH is a not-for-profit pharmaceutical company, representing a new model for development and supply of pharmaceuticals in global health. The organisation is committed to making moxidectin tablets, 2 mg, available at cost-plus pricing (i.e with no profit) for use in low- and middle-income countries. The cost of moxidectin production is also de-linked from the financing of its development. Therefore, only production costs plus a cost to cover administrative expenses will be required to ensure the sustainability of MDGH's supply of moxidectin.

Moxidectin tablets, 2 mg, available in bottles of 500, are US FDA inspected, quality assured and approved and can be procured on-demand. The current batch production of 1.9 million treatments (at an 8 mg dose) will be further optimised to support MDA program roll out in multiple countries. A shift from on-demand to routine manufacture and to facilitate increased production capacity requires information from the field regarding the priority use cases for moxidectin and anticipated demand from countries, as tooling and manufacturing upgrades may be required to produce the necessary volumes. Hence, discussions with and decisions by the community of stakeholders working for onchocerciasis elimination will determine how moxidectin will be used to help achieve elimination goals and inform the potential demand. This information will enable MDGH to anticipate and prepare with relevant partners for an increase in production capacity.

At the current production capacity of 1.9 million treatments per year, the proposed price for moxidectin per 8 mg dose (4 x 2 mg tablets) for onchocerciasis and lymphatic filariasis will be US$1.56. MDGH anticipates that, with production scaled to approximately 30.6 million (8 mg) treatments, the cost per 8 mg dose will reduce by more than half (excluding the cost of tooling and manufacturing upgrade that would be required). The price quoted is Ex Works, meaning cost associated with transporting the goods from the site of manufacture to the point of delivery is not included.

In the retail market, ivermectin tablets can be purchased from various sources, including a WHO prequalified supplier such as Edenbridge, with a declared value of US$83.00 for 20 ivermectin 3 mg tablets (US$4.15/tab). An article from Hernando et al. published in 2016(36) estimated the cost of a generic ivermectin to be US$0.70 for a 9 mg dose (3 tablets of ivermectin 3 mg) although the source was not stated. Other, cheaper sources of ivermectin are available, though they are not prequalified/SRA-inspected and their quality standards are uncertain. These figures are based on retail market prices and may vary significantly. The Health Action International Database of medicines prices, availability, affordability, and price components does not reference the price of ivermectin however when consulting national pricing sources, an ivermectin 3 mg tablet costs US$8.18 in Australia (according to the Pharmaceutical Benefit Scheme website), or US$2.36 per tablet in France (as per the Health Insurance website).

In 1987, Merck committed to donating ivermectin to help eliminate river blindness. This commitment expanded in 1998 to include the treatment of lymphatic filariasis in African countries and Yemen. Over 35 years, the Mectizan® Donation Program has grown from 0.3 million treatments to 376.4 million treatments in 2023, corresponding to approximately 1.355 billion tablets of ivermectin per annum. While the actual cost of this ivermectin treatment is not publicly known, the declared market value of the donated treatment is US$4.50 per treatment, and Merck benefits from a tax exemption from the US government for this donation(36).

While MDGH's price for moxidectin is relatively low, comparisons to a product such as ivermectin provided by the company free of charge for onchocerciasis treatment programmes will be made. However, the cost for the medicine should be evaluated in the context of overall costs for continued country MDA programs, including the inputs from implementing partners, and in comparison to other strategies that might be used to help achieve elimination goals. In their updated work published in 2024, Turner et al(20) estimated the economic cost of annual Community Directed Treatment with Ivermectin (aCDTI) or annual Community Directed Treatment with Moxidectin (aCDTM) strategy to be US$50,535

per 100,000 individuals. Recent modelling suggests that using annual moxidectin could reduce the number of MDA cycles needed to reach disease elimination (Figure 4). As a result, the overall programmatic costs associated with MDA over the reduced time period could also be significantly reduced Table 7. For example, assuming minimal coverage in areas with 50% baseline disease prevalence, aCDTM would, with 90% probability, reduce by 20 years the time to achieving elimination of transmission (EoT_{90}) compared to aCDTI, which in turn would translate to a reduction of programmatic costs by 36%.

Figure 4: Projected program durations needed to achieve 90% probability of Elimination of Transmission (EoT90) for the different treatment strategies*(20)

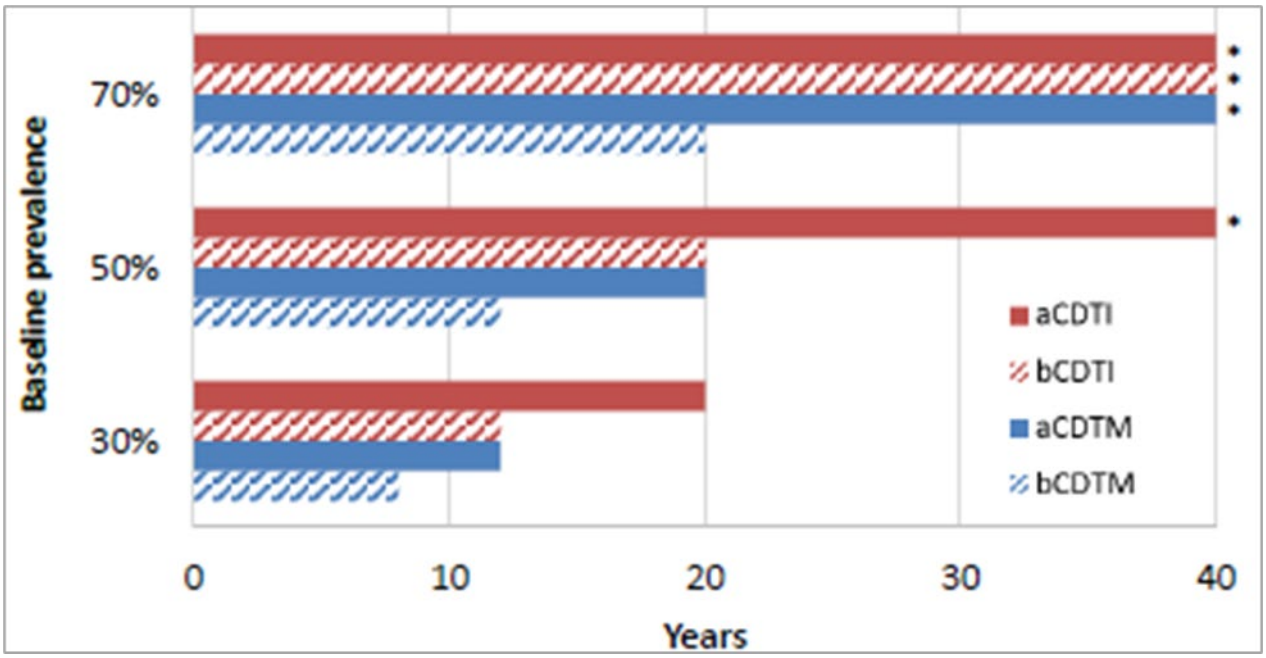


Table 7: Treatment duration (in years) and relative cost (in percent) compared to aCDTI*(20)

Strategy	Baseline prevalence		
	30%	50%	70%
aCDTI	20 (0%)	40+ (0%)	40+ (0%)
bCDTI	12 (+7%)	20 (+3%)*	40+ (+60%)*
aCDTM	12 (–33%)	20 (–36%)*	40+ (0%)*
bCDTM	8 (–25%)	12 (–31%)*	20 (+3%)*

*assuming that ivermectin has half the magnitude of the permanent sterilizing effect compared to moxidectin.

These projections remain sensitive to assumptions regarding the relative permanent adult worm sterilizing effects of moxidectin compared with ivermectin and the change in total delivery costs when the treatment frequency is increased or decreased. However, in the majority of potential use settings, moxidectin has been shown to meaningfully reduce times to elimination and/or the overall programmatic costs compared with the ivermectin strategies currently in use. This is indicative of cost-effectiveness, especially in the context of production of moxidectin at scale.

MDGH continues to work collaboratively with partner organisations to identify ways to finance the supply of moxidectin for use in areas of endemic countries identified as needing a more effective strategy

to accelerate and/or reach elimination of onchocerciasis and/or LF. Licensing arrangements to quality-assured manufacturers in endemic countries are also being evaluated.

11. REGULATORY STATUS MARKET AVAILABILITY AND PHARMACOPEIAL STANDARDS

11.1. Regulatory status

Moxidectin has been approved by the US FDA for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older. The current approved prescribing information for use of moxidectin tablets for onchocerciasis is available at www.fda.gov/drugsatfda. A supplemental NDA to request amendment of the US label to extend the onchocerciasis indication to include younger children (4 years and older) was submitted in August 2024, with a decision from the US FDA anticipated by March 2025.

A Marketing Authorisation Application was submitted to the Ghana Food and Drugs Authority in August 2024 to support the use of moxidectin in onchocerciasis elimination programmes in individuals 4 years and older. An expedited review by the Ghana Food and Drugs Authority is expected to facilitate commencement of a pilot moxidectin MDA programme in Ghana in January 2025.

It is MDGH's intention to engage with the WHO Pre-Qualification Team to support registration of moxidectin for onchocerciasis in endemic countries. An invitation for submission of an Expression of Interest for evaluation is anticipated following commencement of the development of a WHO treatment guideline for moxidectin use in onchocerciasis and lymphatic filariasis.

In addition, MDGH received advice from the WHO in September 2023 as part of the pilot Coordinated Scientific Advice procedure on the most direct and appropriate regulatory and/or policy route(s) to supporting the registration, importation and use of moxidectin in national lymphatic filariasis elimination programmes. As a result, MDGH is considering applying for WHO prequalification via the full assessment pathway to support moxidectin use for the treatment of lymphatic filariasis.

11.2. Market availability

Moxidectin 2 mg, currently produced with lead time and as required in bottles of 500 tablets, supports the implementation of disease elimination programs and clinical trials. As the use cases for moxidectin become more defined, and in collaboration with its funding partners, MDGH will scale up production capacity to meet the growing demand from endemic countries. This may require prioritisation of use cases and/or working with specific priority countries in order to balance demand and supply capacity ramp up in the near term.

11.3. Pharmacopeial standard

Moxidectin drug substance is manufactured to current Good Manufacturing Practice (GMP) standards by Livzon New North River Pharmaceutical Co. using the manufacturing method as per Livzon's current European Directorate for the Quality of Medicines & Healthcare Certificate of Suitability (CEP) for moxidectin for veterinary use. The manufacture and testing of the moxidectin drug substance produced according to the CEP is identical to that for the US FDA authorized drug product. The moxidectin drug substance consistently meets the requirements of the US Pharmacopeia and European Pharmacopeia monographs.

Moxidectin finished product is an immediate-release uncoated tablet for oral use containing 2 mg of moxidectin which is manufactured to current GMP standards and meets in-house specifications as per NDA210867 which has been approved by the US FDA.

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ANNEXES

Annex 1: Letters of Support

GHANA HEALTH SERVICE
HEADQUARTERS

PMB, Ministries - Accra
Digital Address: GA-144-5506

Quote this number and date on all correspondence

My Ref. No: GHS/PHD/NTD.001/2024

Your Ref. No:

Date. 08 October 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

This letter is provided by the Ghana Health Service through the Neglected Tropical Diseases Control Programme in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission.

The Ghana Health Service through the Neglected Tropical Diseases Programme enhances planning for results, resource mobilization and financial sustainability of the national NTD Programme. The NTD programme is mandated to scale up access to interventions, treatment, and system capacity building. It enhances NTD evaluation, surveillance, operational research and strengthens government ownership, advocacy, coordination, and partnerships

Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions. Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of these diseases.

Yours sincerely,

DR. FRANKLIN ASIEDU-BEKOE
DIRECTOR PUBLIC HEALTH
FOR : DIRECTOR GENERAL

UNIVERSITY OF HEALTH AND ALLIED SCIENCES
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OFFICE OF THE VICE CHANCELLOR

My Ref: VC/GA/5 October 15, 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

LETTER OF SUPPORT- INCLUSION OF MOXIDECTIN ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES

This letter is provided by University of Health and Allied Sciences (UHAS), Ho, Ghana in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission.

For over a decade, UHAS has been at the forefront of addressing Neglected Tropical Diseases (NTDs) in Ghana and beyond. Our multifaceted approach encompasses research, implementation of prevention and control programs, and support for national NTD control initiatives. Our faculty members have also served as scientific advisors across all spheres of the NTD community. The Onchocerciasis Chemotherapy Research Centre (OCRC) at UHAS has conducted numerous Phase 2 and Phase 3 clinical trials for Ivermectin and Moxidectin over the years.

Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions.
Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin,

moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of these diseases.

Yours faithfully,

Professor Lydia Aziato
Vice Chancellor

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30329-4027

28 October 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

The Centers for Disease Control and Prevention (CDC) understands that Medicines Development for Global Health (MDGH)'s has applied for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission. The Division of Parasitic Diseases and Malaria has performed operational research to support neglected tropical diseases elimination and control programs for decades, supporting the development of new diagnostics, strategies to improve program impact, and surveys to assess program impact. Personnel in the division provide technical input to discussions at a number of WHO technical groups, including serving as the chair of the WHO Onchocerciasis Technical Advisory Subgroup, which has reviewed much of the moxidectin efficacy and safety trial data.

Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions.

Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy for more sustained suppression of skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older. The sustained suppression may accelerate progress towards the WHO interruption of transmission targets for onchocerciasis described in the WHO Road Map for Neglected Tropical Diseases 2021-2030.

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc prior to completion of these studies

will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission once the studies are completed.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries.

Yours sincerely,

Paul T. Cantey, MD, MPH
Chief, Parasitic Diseases Branch
Division of Parasitic Diseases and Malaria
U.S. Centers for Disease Control and Prevention
1600 Clifton Rd, MS 16-4
Atlanta, GA 30329
+1 404-718-4735
Gdn9@cdc.gov

16 October 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

This letter is provided by the Global Institute for Disease Elimination (GLIDE) in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) as an alternative tool for the elimination of onchocerciasis transmission.

GLIDE is a global health institute based in Abu Dhabi, focused on accelerating the elimination of preventable infectious diseases of poverty: currently, malaria, polio, lymphatic filariasis, and river blindness, by 2030 and beyond. The Institute works to works to elevate awareness and engagement, advance elimination strategies, and foster and scale innovation in partnership with national and international stakeholders, building on country ownership and local solutions.

Onchocerciasis (river blindness), caused by the filarial worm species *Onchocerca volvulus*, is a vector-borne neglected tropical disease (NTD) of public health and socioeconomic concern. Onchocerciasis is targeted in the WHO 2030 NTD Roadmap for elimination of transmission, with challenging targets for achieving this goal in at least 12 endemic countries by 2030[1].

For the last 35 years, the onchocerciasis community has relied on mass drug administration (MDA) with ivermectin (with or without vector control) to reduce the burden of disease and to control the transmission of infection. Significant reduction in the impacts of onchocerciasis have been achieved with annual distribution of ivermectin, but some communities continue to struggle to progress towards elimination.

As early as 2015[2], moxidectin was identified as one of the promising alternative treatments for accelerating onchocerciasis elimination in Africa. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

While MDGH is completing studies that provide additional data on the safety of moxidectin use in endemic communities and in children, inclusion of moxidectin on the WHO EML will send a clear signal to onchocerciasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

[1] Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030, World Health Organisation, 2021.
[2] Report of the consultative meetings on Strategic Options and Alternative Treatment Strategies for Accelerating Onchocerciasis Elimination in Africa, APOC, WHO, Dec 2015

Abu Dhabi Global Health Data Hub | P.O. Box 764641 | Abu Dhabi, United Arab Emirates | +971 2 676 5252

Inclusion in the EML is an essential step to enabling both sustainable access and implementation in onchocerciasis endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of this disease.

Yours sincerely,

Simon Bland, CBE
Chief Executive Officer

Abu Dhabi, United Arab Emirates | P.O. Box 764641 | +971 2 6705 122

Unité Mixte Internationale UMI233-U1175
« Recherches Translationnelles sur le VIH et les Maladies Infectieuses »
TransVIHMI

Docteur Michel BOUSSINESQ, MD, PhD
Directeur de Recherche (DR1)
Neglected Tropical Diseases Group

IRD – UMI 233
911 avenue Agropolis, BP 64501
34394 Montpellier Cedex 5, France
Tél : (33) 4 67 41 64 41 ; Fax : (33) 4 67 41 61 46
email : michel.boussinesq@ird.fr

Montpellier, 4 October 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

This letter is provided by myself, Dr. Michel Boussinesq, in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) as an alternative tool for the elimination of onchocerciasis transmission.
I am a researcher at the Institut de Recherche pour le Développement (IRD), a French public research establishment operating under the joint authority of the Ministry for Higher Education and Research and the Ministry for Foreign Affairs. The IRD is a multidisciplinary institute and upholds the specific nature of its approach by conducting research that is in line with major issues in development.
I have worked for 35 years in the Health Department of IRD and my research focusses on the clinical and epidemiological aspects of onchocerciasis and other filarial diseases in Central Africa. I have also conducted, with my group and collaborators in Cameroon, Congo and DRC, a number of clinical trials aimed at accelerating elimination of these diseases and preventing serious adverse events that may occur after antifilarial treatment.
Onchocerciasis (river blindness), caused by the filarial worm species *Onchocerca volvulus*, is a vector-borne neglected tropical disease (NTD) of public health and socioeconomic concern. Onchocerciasis is targeted in the WHO 2030 NTD Roadmap for elimination of transmission, with challenging targets for achieving this goal in at least 12 endemic countries by 2030[1].
For the last 35 years, the onchocerciasis community has relied on mass drug administration (MDA) with ivermectin (with or without vector control) to reduce the burden of disease and to control the transmission of infection. Significant reduction in the impacts of onchocerciasis have been achieved

[1] Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030, World Health Organisation, 2021.

with annual distribution of ivermectin, but some communities continue to struggle to progress towards elimination.

As early as 2015[2], moxidectin was identified as one of the promising alternative treatments for accelerating onchocerciasis elimination in Africa. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

While MDGH is completing studies that provide additional data on the safety of moxidectin use in endemic communities and in children, inclusion of moxidectin on the WHO EML will send a clear signal to onchocerciasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML is an essential step to enabling both sustainable access and implementation in onchocerciasis endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of this disease.

Yours sincerely,

M. Boussinesq
Director of Research, IRD

[2] Report of the consultative meetings on Strategic Options and Alternative Treatment Strategies for Accelerating Onchocerciasis Elimination in Africa, APOC, WHO, Dec 2015

Sightsavers

6 October 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

This letter is provided by Sightsavers in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission. Sightsavers Inc. (www.sightsaversusa.org) is a registered 501 (c)(3) nonprofit organization (EIN 47-4657747) that works in more than 30 developing countries to prevent blindness, restore sight and advocate for social inclusion and equal rights for people with disabilities. Elimination of river blindness (onchocerciasis) and lymphatic filariasis (LF) are therefore at the core of Sightsavers vision of a world where no one is blind from avoidable causes and where people with disabilities are able to participate equally in society.

Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions.

Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of these diseases.

Yours sincerely,

Simon Bush
Director Neglected Tropical Diseases, Sightsavers

UNIVERSITÄT BONN

ukb universitäts klinikumbonn
Institut für Medizinische Mikrobiologie, Immunologie und Parasitologie

Institut für Med. Mikrobiologie, Immunologie und Parasitologie (IMMIP)
Universitätsklinikum Bonn, Venusberg-Campus 1, 53127 Bonn

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27

Bonn, 18. Oktober 2024

Letter of Support for inclusion of moxidectin in the WHO Essential Medicines List 2025

Dear Sir or Madam,

This letter is provided by Institute for Medical Microbiology, Immunology and Parasitology of the University Hospital Bonn, Germany in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission.

The development of new drugs and regimens against onchocerciasis and lymphatic filariasis has been a major preclinical and clinical research activity of my team. Preclinical studies, supported by the Drugs for Neglected Disease initiative (DNDi), the Bill & Melinda Gates Foundation and DZIF, have been conducted in collaboration with partners from industry and academia, e.g., Washington University, St. Louis, MO, USA and Eisai Co., Ltd., leading to the discovery of several new preclinical candidates, three of which were recently tested in "first-in-human" studies. The Institute for Medical Microbiology, Immunology and Parasitology collaborates with many partners in Cameroon, Ghana, Tanzania and has performed more than 15 GCP compliant clinical trials.

I am chair of the German Network against Neglected Tropical Diseases (DNTDs, www.dntds.de), which acts as a contact for the German Federal Government; advising the various ministries involved in the implementation of the Federal Government's obligations committed to in the Kigali Declaration, the G7 and G20 declarations, and the UN Sustainable Development Goals and the Global Health Strategy. In 2018 I was member of the Meeting of the Expert Panel on Filarial Infections: Establishing Post-2020 Priorities for the Global Programme to Eliminate Lymphatic Filariasis (GPELF). Since 2020 I have been a member of the WHO Diagnostic Technical Advisory Group (DTAG) for Neglected Tropical Diseases, subgroup lymphatic filariasis.

Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and

DZIF
Deutsche Zentrum für Infektionsforschung e.V.

Univ.- Prof. Dr. med. Achim Hörauf
Direktor

Standortkoordinator DZIF Bonn-Köln
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Universitätsklinikum Bonn
Venusberg-Campus 1
53127 Bonn

Ihr Weg zu uns
auf dem UKB-Gelände:
DEXP23
Gebäude 63

hydrocele. Both conditions primarily affect impoverished populations in tropical regions.

Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of these diseases.

Yours sincerely,

Professor Achim Hörauf
Director

Universitätsklinikum Bonn
Institut für Med. Mikrobiologie,
Immunologie und Parasitologie
Venusberg-Campus 1
53127 Bonn

Prof Joseph KAMGNO
CEO
P.O. Box 5797 Yaoundé
Joseph.kamgno@ismcm.org

October 4, 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

This letter is provided by Prof Joseph Kamgno from the Higher Institute for Scientific and Medical Research in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission. The ISM, formerly known as CRFilMT, has been working for some 20 years on Neglected Tropical Diseases, especially onchocerciasis, lymphatic filariasis and loasis. We are well placed to talk about NTDs, given our experience in the field in Sub-Saharan Africa in general and Central Africa in particular.

Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions.

Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of these diseases.

Yours sincerely,

ISM
Higher Institute for Scientific and Medical Research
285 Steet 1,411, Fouda Quarter, P.O. Box 5797 Yaounde, Cameroon / E-mail: joseph.kamgno@ismcm.org / Site Web: www.ismcm.org

October 7, 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

I am writing this letter in in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission.

I am writing in my role as the Director of the Neglected Tropical Diseases Support Center (NTD-SC) at the Task Force for Global Health. The Task Force for Global Health, an independent, 501(c)3, nongovernmental organization based in Georgia, USA is recognized by WHO as an official Non-State Actor. The programs of the Task Force focus on eliminating diseases and protecting populations The NTD-SC has a specific focus on supporting operational research to improve the public health impact of NTD control and elimination programs. We value the lives of all people and believe they should have equitable access to the services that lead to healthier lives. We have been long-term supporters of the work of Medicines Development for Global Health because of their resolute commitment to similar goals and their innovative approaches to developing products to reduce the burden of neglected diseases.

Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions. Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received

approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. The inclusion of moxidectin in the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis-affected countries that they will have access to an alternative, effective treatment with the potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to facilitate elimination of these diseases.

I would be pleased to provide further information if required.

Sincerely yours,

Dr Patrick Lammie
Director, Neglected Tropical Diseases Support Center,
The Task Force for Global Health
330 W. Ponce de Leon Ave.,
Decatur, GA, 30030

Email: plammie@taskforce.org
Phone: 1-404-687-5613

4th October 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27

Dear Sir or Madam,

This letter is provided by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseaeses (TDR), in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission.

TDR has had decades of involvement with the development of moxidectin, having sponsored the key trials in Africa critical to the registration of this drug, before transferring responsibility to MDGH as a more suitable organisation to bring moxidectin to registration and widespread use.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of these diseases.

Yours sincerely,

Professor John Reeder
Director, Department of Research for Health and
Director, UNICEF/UNDP/World Bank/WHO Special
Programme for Research and Training in Tropical Diseases (TDR)
World Health Organization, Geneva.

October 17, 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

This letter is provided by the END Fund in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission. The END Fund is a private philanthropic fund dedicated to eliminating neglected tropial diseases.

Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions. Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older.

2 Park Ave, 28th floor | New York, NY | 10016 | USA
end.org

MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of these diseases.

Yours sincerely,

Jamie Tallant
Associate Vice President
Team Lead for the Reaching the Last Mile Fund

2 Park Ave, 18th floor | New York, NY | 10016 | USA

end.org

CENTRE DE RECHERCHE
EN MALADIES TROPICALES
CECA/20 RETHY
Province de l'Ituri
République démocratique du Congo

16th October, 2024

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

Dear Sir or Madam,

This letter is provided by "*the Centre de Recherche en Maladies Tropicales*" (CRMT) in support of Medicines Development for Global Health (MDGH)'s application for the inclusion of moxidectin on the WHO Model List of Essential Medicines (EML) and WHO Model List of Essential Medicines for children (EMLc) as an alternative tool for the elimination of onchocerciasis and lymphatic filariasis transmission. CRMT has been involved in tropical diseases research activities with the support of various partners. In 2009, WHO/TDR initiated phase III clinical trial of moxidectin at CRMT together with 3 other research centers in the Democratic Republic of Congo, Ghana and Liberia which was completed in 2013. Additionally, CRMT participated in other entomological and epilepsy onchocerciasis related studies as well as in plague which is endemic in the area. Onchocerciasis, or river blindness, leads to severe visual impairment and skin disfigurement, while lymphatic filariasis can result in debilitating lymphedema and hydrocele. Both conditions primarily affect impoverished populations in tropical regions.

Despite substantial progress towards elimination of these diseases with ivermectin and ivermectin combination regimens, approximately 246 million people still require preventive chemotherapy against onchocerciasis and 794 million people require preventive chemotherapy against LF.

Moxidectin has been identified as one of the promising alternative treatments for accelerating elimination of filarial diseases. Having completed the phase 3 clinical trial showing a similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin, moxidectin received approval from the US Food & Drug Administration (FDA) in 2018 for treatment of onchocerciasis in people aged 12 years and older. MDGH and research partners are currently completing studies that provide additional data on the safety of moxidectin use for in endemic communities and in children, as well as building the evidence base for efficacy in LF. Inclusion of moxidectin on the WHO EML and EMLc will send a clear signal to onchocerciasis and lymphatic filariasis affected countries that they will have access to an alternative, effective treatment with potential to provide a solution for areas of continued transmission.

Inclusion in the EML and EMLc is an essential step to enabling both sustainable access and implementation in onchocerciasis and lymphatic filariasis in endemic countries and we are supportive of the application for inclusion of moxidectin as an alternative tool to progress elimination of these diseases.

Yours sincerely,

Yours sincerely,

Tony UKETY, MD, MPH
Medical Director

CRMT/CECA/20 : HGR Rethy, Zone de Santé de Rethy, Téléphone : 0822400101

Medicines Development for Global Health Moxidectin EML Application

Annex 2: WHO paediatric quality product profile assessment tool (pQPPAT)

Product name (INN): Moxidectin
EMLc section(s): 6.1.2 Antifilarials
Route of administration: Oral
Dosage form and strength(s): 2mg tablet

Evaluation for WHO EMLc paediatric population, birth to 12 years.

Attribute	Result	Comparison to Target and Risk Assessment	Score	Additional considerations/information
Target population (age)	Patients aged 4 years and older.	Moderate risk/issues; partially meets target. Suitable for most of the API indicated paediatric population.	2	
Dose and dose flexibility	Two distinct dosage levels based on age groups: 8 mg moxidectin dose (four 2 mg tablets) in all patients aged 8 years and older, and 4 mg moxidectin dose (two 2 mg tablets) in children aged 4 to 7 years.	Low risk/no issues; meets target. Able to easily measure and administer the required doses to all patients.	3	
Patient acceptability: 0-5 years	Single dose. Palatable flavour.	Moderate risk/issues; partially meets target. Tablet formulation unsuitable for patients less than 4 years of age.	2	Approximately 700 children aged 4 to 11 years have been dosed with moxidectin 2mg tablets in studies MDGH-MOX-1006 (A pharmacokinetic and safety study of moxidectin to identify an optimal dose for treatment of children 4 to 11 years (NCT03962062)) and MDGH-MOX-3002 (Safety of a single dose of moxidectin compared with ivermectin in individuals living in onchocerciasis endemic areas and in individuals living in onchocerciasis endemic areas with high levels of lymphatic filariasis co-endemicity receiving concomitant albendazole (NCT04311671)). No issues related to patient acceptability in this age group were reported in either study.
Patient acceptability: 6-12 years	Single dose. Tasteless to mildly sweet in flavour. Easy to swallow (Tablet size: Width = 4.55 mm, Length = 8.13 mm and Thickness = 2.55 mm)	Low risk/no issues; meets target. Acceptable for this age group.	3	
Excipients safety	Moxidectin tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose anhydrous, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. Tablets do not include presevatives, co-solvents and solvents, sweeteners, or colorants.	Low risk/no issues; meets target. All ingredients are commonly used, well-tolerated tabletting excipients with good safety records.	3	
Administration considerations	Taken orally with or without food.	Low risk/no issues; meets target. No manipulation required, easy to measure and administer required doses (HCP use).	3	
Stability, storage conditions and primary packaging material	Store below 30°C (86°F). Protect from light. Each high-density polyethylene bottle contains 500 tablets. Once open, the full contents of the container should be used within 24 hours with any unused content discarded.	Moderate risk/issues; partially meets target. May require refrigeration depending on climate and has a short in-use shelf life.	2	
Registration status	Approved by US FDA for use in patients aged 12 years and older. Supplementary NDA submitted to US FDA to include patients aged 4 to 11 year of age in label submitted in August 2024, outcome expected by March 2025. Application for registration of moxidectin for the treatment of onchocerciasis in children (4 years and older) and adults has been submitted to the Ghana Food and Drug Authority (WHO Maturity level 3), an outcome is expected by the end of 2024.	Low risk/no issues; meets target. Approved by at least one Stringent Regulatory Authority for patents aged 12 years and older. Approval by Stringent Regulatory Authority anticipated for patients aged 4 to 11 years of age in early 2025.	3	

Overall Conclusions

Moxidectin 2 mg oral tablets are approved by the US FDA for the treatment of onchocerciasis due to Onchocerca volvulus in patients aged 12 years and older, demonstrating compliance with rigorous regulatory standrads. A supplementary NDA to include patients aged from 4 to 11 years of age in the US FDA label was submitted in August 2024, with a decision by the US FDA expected by March 2025. This paediatric quality product profile assessment was conducted based on the anticipated US FDA label from March 2025.

Overall moxidectin 2 mg oral tablets are acceptable for the paediatric population aged from 4 years and older. The current 2 mg tablet formulation is suitable for swallowing by children aged 4 years of age and older. Tablet strength allows for easy measurement and administration of required doses to all patients without the need for manipulation or complex procedures. There are no issues with palatability. The excipients used in the product have an acceptable safety profile, posing no known or potential concerns. The product requires refrigeration in some settings, and has a short in-use stability.

Risk Scores		
	No or insufficient information	0
	High risk/issues; does not meet target	1
	Moderate risk/issues; partially meets target	2
	Low risk/no issues; meets target	3

Date of review: 29-Oct-24
Prepared by: Medicines Development for Global Health

Summary

Product name (INN): Moxidectin
EMLc section(s): 6.1.2 Antifilarials
Route of administration: Oral
Dosage form and strength(s): 2mg tablet

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Information sources

Product name (INN): Moxidectin

EMLc section(s): 6.1.2 Antifilarials

Route of administration: Oral

Dosage form and strength(s): 2mg tablet

Add links or references to key information sources here.
Moxidectin 2 mg Tablets US FDA Prescibing Information https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210867s003lbl.pdf

Date of review: 29-Oct-24

Prepared by: Medicines Development for Global Health