Report of the fifth meeting
of the Onchocerciasis
Technical Advisory Subgroup

Virtual meeting
9–10 December 2021
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Abbreviations and acronyms

CDC United States Centers for Disease Control and Prevention
CDTi community-directed treatment with ivermectin
DBS dried blood spots
ELISA enzyme-linked immunosorbent assay
FDA United States Food and Drug Administration
MDA mass drug administration
mf microfilariae
OEM onchocerciasis elimination mapping
OTS Onchocerciasis Technical Subgroup
PCR polymerase chain reaction
RAPLOA rapid assessment procedure for *Loa loa*
RDT rapid diagnostic test
SAE serious adverse event
TaNT test-and-not-treat
TFGH The Task Force for Global Health
WHO World Health Organization
Executive summary

The fifth meeting of the Onchocerciasis Technical Advisory Subgroup (OTS) of the World Health Organization (WHO) was held virtually on 9–10 December 2021. The main outcomes of the meeting are summarized below.

Ov16 diagnostic tools

Ov16 serology can be used for mapping. The performance of the Ov16 rapid diagnostic test (RDT) with eluted dried blood spots (DBS) compared favourably with the Standard Diagnostics (SD) Bioline enzyme-linked immunosorbent assay (ELISA), with similar sensitivity and better specificity. Use of the Ov16 RDT with eluted DBS avoids the inconsistency issues seen across ELISA results; it is also an easier assay to run. The DBS have to be eluted in the buffer overnight and tested the next day. The work should be conducted in a protected space (either in the central laboratory or in the field) and the results read at 24 h. The process can take up to 3 days. Evidence from skin snip polymerase chain reaction (PCR) suggests that real-time quantitative PCR (qPCR) demonstrated improved detection with qPCR over PCR. New improved serological tools are needed to properly monitor all stages of onchocerciasis elimination programmes.

Mapping

Exclusion mapping involves identifying areas that are not environmentally suitable for blackfly breeding, based on careful review of geographical and programmatic data. Onchocerciasis elimination mapping (OEM) is necessary in environmentally suitable areas that are unmapped or untreated for onchocerciasis. WHO should publish guidance on conducting OEM to support countries in accelerating implementation. Completing OEM and starting treatment in areas of active transmission are critical to achieving elimination and meeting the targets of the road map for neglected tropical diseases 2021–2030 (“the road map”). OEM should start with the highest risk areas first.

Lymphatic filariasis and onchocerciasis co-evaluation

Co-evaluation of both diseases is possible and cost efficient. Some activities can be integrated, and others implemented in a coordinated manner. A field manual is required to guide countries.

Mapping and treatment in Loa loa co-endemic areas

For areas in which onchocerciasis and loiasis are co-endemic the mapping and treatment algorithm presented at the fifth meeting is accepted by the OTS and is now available for field testing by programmes. The algorithm indicates that MDA can be implemented in areas of low Loa loa endemicity; in areas of moderate or high endemicity further mapping is required before a decision on safety of MDA treatment or test-and-not-treat (TaNT) can be made. This algorithm defines areas of low risk (prevalence of microfilariae [mf] > 5 – < 20%), moderate risk (20–40%) and high risk (> 40%).

A Loa loa antibody test is now available. This rapid diagnostic test can be used at any time of the day and the results read after 20 min. With the availability of this new test, a two-stage approach is proposed
for mapping the prevalence of *Loa loa* in areas where the risk (i.e., the prevalence of high intensity *Loa loa* infections) is uncertain. The first stage calls for representative sampling using the test. If the results alone do not lead to clear risk categorization as either low risk (i.e., safe for community-directed treatment with ivermectin (CDTi)) or high risk (i.e., requiring TaNT) then a follow-up survey using the LoaScope in uncertain areas is required. Applying this two-stage approach in Gabon showed that similar results can be achieved as compared with testing everyone by LoaScope, but with significant saving of resources. The TaNT strategy successfully enables treatment of onchocerciasis in high endemicity settings without serious adverse events (SAEs). The cost of individual testing and treating is very high compared with MDA and implementation at large scale is therefore limited. Availability of LoaScope is also a challenge that must be addressed if the strategy is to be implemented by national programmes.

**Revising the stop MDA threshold**

Operational research is ongoing to inform a revised threshold for stopping MDA. The thresholds being tested are based on the average seroprevalence in the evaluation area, calculated from prevalence measured in selected first-line and other villages. There is a need to look at the average but also to pay attention to signals in individual villages. It may be necessary to adapt the methodology to consider village-level prevalence, to avoid missing areas of ongoing transmission. Conducting pre-stop MDA surveys in areas of higher onchocerciasis risk could help reduce the cost of the evaluations. Pre-stop MDA surveys are prevalence surveys conducted in villages known to have higher prevalence at baseline. If pre-stop MDA surveys demonstrate prevalence below a certain threshold the evaluation unit can move to the full-stop MDA survey. Diagnostics to be used, age groups and thresholds should be informed by operational research.

**Moxidectin**

Three studies are ongoing to specifically address paediatric dose finding, annual or biannual treatment, and single dose safety. A study on safety in *Loa loa* endemic areas is also in preparation. It was noted that in the phase III study around 4% of individuals experienced SAEs after treatment with either ivermectin or moxidectin in non-*L. loa* endemic settings during the first 6 months of the up to 18 months of follow up. None of these were assessed as ivermectin or moxidectin related. Moxidectin has been approved by the United States Food and Drug Administration (FDA) for use in those aged 12 years and older. WHO should review the available evidence and provide a recommendation on the programmatic use of moxidectin. Until approval for paediatric use, use of moxidectin via MDA will be challenging. The OTS-supported moxidectin pilot implementation studies and specifically the plans of The End Fund and the national programmes for moxidectin implementation studies in areas of Ethiopia, Mali and Senegal where countries are facing specific obstacles towards elimination of *Onchocerca*. Pilot implementation studies respond to the required actions outlined in the road map.

**Verification dossier**

Onchocerciasis verification dossiers require collection of all available information on the epidemiology and entomology of *O. volvulus*, as well as clinical data, in each area with past transmission in a country. Mapping, coverage, monitoring, evaluation and surveillance data are critical. Methods used for surveillance must be described in detail. Publications in peer review journals must be encouraged as part of the history of elimination in a country. The role and composition of National Onchocerciasis Elimination Committees have to be described. The reporting and management system for SAEs should also be included. WHO should provide a template for countries to support preparation of their dossiers. Countries should work on preparing the dossier as the programmes are still ongoing and not wait until elimination is achieved in order to have proper inclusion of all the required information documenting the process of elimination.
1. Introduction

Due to the ongoing coronavirus disease (COVID-19) pandemic, the fifth meeting of the OTS was held virtually on 9–10 December 2021. The participants (listed in Annex 1) were welcomed and commended for the progress achieved despite the pandemic. The role of the onchocerciasis community in driving progress was highlighted before the next steps for controlling transmission of the disease were outlined.

1.1 Opening remarks

The meeting was opened by Dr Gautam Biswas, Director ad interim, WHO Department of Control of Neglected Tropical Diseases, on behalf of Dr Mwelecela Malecela, who thanked the participants for joining.

Dr Biswas began by recognizing the accomplishments of the onchocerciasis community over the past decades. Countries endemic for onchocerciasis have strived to make progress in spite of the disruptions caused by the COVID-19 pandemic. Notwithstanding these challenges, 112 million people received treatment in 2020, a reduction of about 27% from the 156 million treated in 2019. To have achieved this progress in the context of the pandemic is commendable. He went on to thank the health workers, health ministries and partners who had made it possible. More than 1.8 million people now live in areas where post-treatment surveillance has been completed and MDA is no longer required. As a result, WHO is hoping to verify 12 countries as free of onchocerciasis transmission and 34 countries as having stopped MDA in at least one transmission zone by 2030.

Dr Biswas observed that support for interrupting transmission remains strong and that WHO continues to engage with stakeholders. Efforts to interrupt transmission must be maintained and high-quality interventions continued on both vector-control aspects and MDA, he underscored, until transmission of the disease is eliminated in each of the endemic countries. Improved guidance tools and systems are in place, but further improvement is still required so that decisions taken can be evidence-based and data-driven.

Next, he set out the four main agenda items for discussion at the meeting: (i) the development of a provisional Loa loa strategy for safe onchocerciasis treatment in areas co-endemic for onchocerciasis and loiasis; (ii) an update on work to revise serological thresholds for stopping MDA for onchocerciasis; (iii) next steps for moxidectin use in onchocerciasis elimination following the verification of four countries for having eliminated onchocerciasis; and (iv) the need to improve the existing dossier requirement for verification of elimination in remaining countries.

Dr Biswas concluded his remarks by commending the partnership among endemic countries, WHO, nongovernmental funding partners and others, as well as the contribution of MSD, whose involvement in funding this endeavour through their donation programme has been crucial.

1.2 Announcements

Dr Paul Cantey, Chair of the OTS, outlined the rationale for rotating committee membership and for maintaining a broad input over time. He thanked the current members for their dedication to moving the operational programme and key questions forward. An announcement on the process for recruiting new members would be made in 2022. Current members wishing to move on should make their intentions known to Dr Maria Rebollo, who has taken over from Dr Sankara as the OTS technical focal point at WHO headquarters.
1.3 Overview of the agenda

Day 1: The first day’s deliberations would review and provide input on strategies for safe treatment of onchocerciasis in areas co-endemic with loiasis.

Day 2: The second day would begin with a session to include updates on work to revise the serological target threshold for stopping MDA for onchocerciasis and provide opportunities for input. The day would include updates on the addition of moxidectin as a tool to achieve elimination of onchocerciasis. A final session would follow to review considerations for WHO’s verification of the development of an elimination dossier.

1.4 Highlights from the fourth meeting

The decisions and recommendations of the fourth (virtual) meeting (28–29 October 2020) (1) are summarized below.

✦ Review of which Ov16 ELISA to use for stopping MDA evaluations

Progress on Ov16 ELISA comparison was limited due to COVID-19:

1. Programmes may continue to use the ELISA that they are already using as long as there is a robust quality assurance system in place.
2. There was no final selection of one ELISA version versus another.

✦ Update on Ov16 serology for mapping

3. The performance of RDT with eluted DBS compared favourably to the SD ELISA, having:
   - similar sensitivity and better specificity;
   - avoids the issue of inconsistency of ELISA results; and
   - easier to run.
4. Programmes should use RDT with eluted DBS for OEM, taking into account:
   - the imperfect specificity of RDT and the algorithm proposed;
   - the availability of protocols for making buffer and eluting DBS, as well as the training video available on the NTD website.

✦ OEM

No new data were available to review in order to inform the strategy.

5. The OTS highlighted that mapping should:
   - occur only in areas where the environment is suitable for blackflies (exclusion mapping);
   - start with the highest risk areas first.

✦ Co-evaluation of lymphatic filariasis and onchocerciasis

A proposed algorithm for co-evaluation of both diseases in different settings was described.

6. Some activities can be integrated, and others implemented in a coordinated manner.
7. Integration will require some flexibility in terms of the current WHO requirements.
8. The algorithm needs stakeholder input and operational research.
Advances in molecular techniques for blackfly PCR

Evidence from skin snip PCR suggested that qPCR demonstrated improved detection with qPCR over PCR. A collaborative group was established to examine the use of qPCR in entomological evaluations.

9. Results indicated that 0-150 qPCR outperformed standard PCR.
10. qPCR is simpler and faster than standard PCR.
11. The 0-150 qPCR developed by the National Institutes of Health should be evaluated in country-run laboratories.
12. OvNDS qPCR could be developed as an independent confirmatory test.

Updates

Updates were given on:

13. plans for biomarker development supported by the Bill & Melinda Gates Foundation;
14. progress on the new WHO onchocerciasis entomology manual (in production); and on
15. new target product profiles for onchocerciasis diagnostics (2).
2. Development of a provisional strategy for safe onchocerciasis treatment

The meeting then heard presentations on three available tools for *Loa loa*, namely:

- serology: Loa antibody rapid test and a preliminary estimation of the risk of SAEs;
- updates on test-and-not-treat strategy; and
- updates on LoaScope algorithm.

There followed a presentation on the algorithm for safe treatment of onchocerciasis in areas co-endemic for *Loa loa*, a general discussion and a focused discussion on the algorithm.

2.1 Review of the available tools

2.1.1 Serology

Dr Marco Biamonte presented a report on the Loa antibody rapid test and a preliminary estimation of the risk of SAEs.

The Loa antibody rapid test is commercially available, with some 38,000 tests in stock. The test, developed in 2017, detects antibodies to a protein expressed by all stages of the *Loa loa* parasite (SXP-1). For details on performance see Pedram et al. (2017) (3). The test was designed to be easy to use in the field. It can be read after 20 min at any time of the day or night. It has been successfully deployed in Nigeria (*n*=9000) and Gabon (*n*=3000).

A trade-off between sensitivity and specificity can be improved through use of a quantitative smart phone intensity reader for the RDT that eliminates weak or false positives. The results using the reader are comparable to ELISA. The smartphone reader proved to be extremely useful too, the meeting heard, for traceability purposes. Complications arose with the smartphone reader due to expense, customs and distribution problems. It was assessed to be suboptimal at scale.

- **Scenario 1:** The RDT can be recalibrated so that the optimal threshold determined in Gabon is at the cusp of what can be seen with the naked eye.
- **Scenario 2:** The Loa antibody rapid test is a pan-IgG test and it is possible that an IgG4 test would be more specific.
To estimate the relationship between seroprevalence and risk of SAEs, three rules of thumb were derived from different data sets. These however come with caveats, so the meeting was advised that caution was required in interpretation:

<table>
<thead>
<tr>
<th>Rule</th>
<th>Antibodies against SXP-1</th>
<th>Circulating mf</th>
<th>High microfilaraemia (&gt; 30 000)</th>
<th>Experienced SAEs</th>
<th>Antibodies against SXP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25% (1 in 4)</td>
<td></td>
<td></td>
<td></td>
<td>0.18% (1 in 560)</td>
</tr>
<tr>
<td>2</td>
<td>5% (1 in 20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>14% (1 in 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If the seroprevalence is: then SAEs per 100 000 treated is:

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

Initial evidence suggests that:

- an antibody test can be used to predict the risk of SAEs;
- acceptable risk needs to be defined and refined;
- even areas with 1% of seroprevalence can give rise to a few SAEs; and
- to detect areas of 1% of antibody prevalence, the test must be ultra-specific (by analogy with the onchocerciasis RDT target product profile) or will need a confirmatory test (e.g., PCR on DBS).

Some counterpoints to the above rules were observed: the rules presented are those based on relatively restricted data sets, for example, and rule 2 was clearly not true in Nigeria. The meeting was asked if any of these rules had been examined in multiple epidemiological settings.

2.1.2 Updates on the test-and-not-treat strategy

The meeting then received updates from Dr Joseph Kamgno on the advances in knowledge on the test-and-not-treat strategy since the last meeting.

With high \( L. \ loa \) microfilarial load there is a risk of SAEs. The objective of this project was to try to isolate those who were infected and treat the rest of the patients without the risk of SAEs. This strategy was developed with the new LoaScope tool. People were tested with the tool and those who had more than 20 000 mf/mL were excluded and the rest of the population was treated.

Dr Kamgno showed the results of first and second rounds of treatment in the Okola district of Cameroon where Loa prevalence rates, as estimated by kriging, are above 40%.

- Treatment coverage was increased between 2015 and 2017, because patients were reassured by the TaNT strategy.
- There was a question over whether it was necessary to treat everyone across the whole year. Results showed that 6981 (> 99.9%) of 6983 individuals treated with ivermectin in 2015 had a \( Loa \ loa \) mf density below the exclusion threshold (20 000 mf/mL) 18 months later (4).
- The concern here was to know how to identify those who were treated the previous year. Only a proportion of patients could be matched between the first and second rounds. Biometric identification of treated subjects using biometry tablets was tried. While there were some limitations due to the quality of the devices (tablets) used to enter the data, the system worked. Biometry registration was found to be the best way to identify those treated the previous year and who could be treated the following year without testing.
Teams are now preparing the implementation of digital registers with biometry to replace paper registers used since the beginning of CDTi.

The advantages of digital registration are:

- easier calculation of therapeutic coverage rates;
- data feedback with much improved quality of data at different levels of the health pyramid;
- useful to follow and sensitize systematic non-compliers and mobile populations; and
- use of this platform for other public health programmes.

Another concern was the expense of delivery, so a strategy of use for community personnel was adopted. It was found that in just 2 days of training, community personnel can successfully implement the TaNT strategy at a lower overall cost.

Dr Kamgno reported that new LoaScopes are now available and will be evaluated for use in forthcoming campaigns.

**Conclusions**

- The TaNT strategy successfully enables treatment of onchocerciasis in settings with high Loa endemicity without SAEs.
- The population understands and trusts the TaNT strategy.
- With very short training, community personnel can successfully implement the TaNT strategy.
- An individual treated with IVM will not need to be retested in the subsequent TaNT campaign.
- Biometric census will be key for TaNT community interventions in general.

### 2.1.3 Shrinking the map: a strategy for *Loa loa* endemic areas that are safe for MDA

Dr Katie Gass and Dr Peter Diggle presented updates on the LoaScope algorithm, summarized as follows:

- The current tools and information to inform decision-making come from current maps, programme data, antibody RDT surveys, LoaScope and geostatistical models.
- These can be used to the estimate risk of SAEs, categorized as:
  - very low risk: treat if onchocerciasis present;
  - moderate or unknown risk: further mapping required; and
  - high risk: use TaNT.
- Two-stage sampling is advised for areas with no history or data on SAEs in order to achieve a more cost-effective use of scarce LoaScope resource without compromising safety. Antibody (AB) screening is cheaper and hence more scalable than LoaScope sampling and is a more sensitive indicator of exposure to Loa.
- Rationale for two-stage sampling:
  - local environment is predictive of Loa prevalence;
  - prevalence at any one location is predictive of prevalence nearby;
  - prevalence is predictive of the proportion of heavily infected individuals;
  - AB response is predictive of LoaScope response.
The prevalence of *Loa loa* antibodies can be used as an initial screening tool to predict areas where the risk of SAEs is low versus high, while the LoaScope, a more specific and direct measure of an individual’s risk, can be used in unacceptably uncertain areas.

Three strategies were compared:

- AB and LoaScope (at the same time),
- AB only, and
- two-stage (AB then LoaScope for uncertain or unknown areas).

The full approach involves testing everyone for AB and LoaScope at the same time. This is the most resource-intensive approach and acts as a “gold standard” relative to which the performances of the other two approaches can be assessed. By taking the two-stage approach, testing for AB first and then following up with LoaScope in uncertain areas, similar results can be achieved to the full approach but with significant saving of resources. These results support the use of a two-stage strategy, in which AB testing is used to identify areas that, with high probability, are safe or unsafe for MDA, followed by LoaScope in uncertain areas.

Third-generation LoaScopes are due to undergo field evaluation. The first 10 devices were delayed for over a year due to supply chain issues. Validation is now planned in Cameroon in the next few months; it is then intended to replicate the Gabon work in two additional co-endemic settings, once 90 additional LoaScopes become available. Potential sites for this operational research field validation of strategy is planned for Angola and the Democratic Republic of the Congo.

### 2.2 Algorithm for safe treatment of onchocerciasis in areas co-endemic for *Loa loa*

Dr Sébastien Pion noted two major paradigm shifts:

The first involves a shift from control to elimination. Control was considered the best that could be done, there was no evidence for elimination, but evidence emerged, and control shifted to elimination. This means everyone must be treated, even those who are *Loa*-infected or at risk. This differs from control approaches, where *Loa* co-endemic areas were avoided as posing an unacceptable risk.

The second shift concerns the existence henceforth of a point-of-care tool capable of identifying people most at risk of SAEs after ivermectin at the point of treatment. Before 2018, the decision to treat or not to treat with ivermectin was made at community level. There was no specific individual profile for SAEs; they occurred in males, females and children. Now, the meeting heard, it is possible to quantify risk at individual level, using LoaScope. This may lead to different ways of considering the best strategy to use.

Risk-mitigation strategies to eliminate onchocerciasis, while minimizing risk for those *Loa loa* co-infected were explored. The meeting heard that there are a number of strategies available to approach elimination of onchocerciasis, depending on whether or not *Loa* is also co-endemic:

- Previously treated onchocerciasis-endemic areas with no history of SAEs can implement CDTi. Untreated onchocerciasis endemic areas with no *Loa* endemicity, based on previous data or recent mapping (RAPLOA 0% or antibody 0%), can also conduct routine CDTi.
- Previously treated onchocerciasis areas where *Loa* is co-endemic, or there is a history of SAEs, could proceed with CDTi if it included a question on previous participation in MDA. All persons who had never received ivermectin or missed the latest round would be tested using a TaNT approach. Reliable records would be required for such an approach.
In onchocerciasis-endemic areas, not previously treated, with moderate endemicity of loiasis, there is an assumed low risk for SAEs. This means areas with RAPLOA more than 0% but less than 40%. However, the relationship between eye worm passage reporting and individual risk of SAEs shows high variability and is not predictive at the individual level. So, in this scenario, TaNT is needed. It is possible to proceed to CDTi in future if low risk (few or no high Loa mf loads) is proven during TaNT.

In onchocerciasis-endemic areas, not previously treated, with high endemicity of loiasis, there is a high risk of SAEs. This means areas with RAPLOA greater than 40%. In such areas, TaNT is the only acceptable approach.

The meeting then heard about the roles and responsibilities of implementing partners.

Responsibility, it was stated, lies with the countries (supported by elimination expert committees), but not all committees are equally strong. Good guidance should come from the international level. This is especially important in complex scenarios of onchocerciasis-endemic areas not previously treated that have moderate endemicity for loiasis, for which criteria and types of information needed for decision-making are needed. Such guidance should be provided in both English, French and perhaps Portuguese.

National ministries of health, the meeting heard, should follow the 2004 TCC/MEC guidelines (5) when using donated medicines and minimize inadvertent treatment of individuals at risk of SAEs. Along with partners, health ministries have responsibility for short-term care of people with SAEs and for providing training for that care to health workers. The community is responsible for the prompt reporting of SAEs. Countries are also expected to take responsibility for long-term sequelae of SAEs.

It was subsequently stated that all data collected using the LoaScope should be collated centrally to refine the community’s understanding of how best to use this tool, to advance local risk assessment and to guide further research. Good communication is required between countries and supranational levels, and possibly among community health workers. Global sharing of outcomes, monitoring of progress and communication will also improve programmes’ power to meet programmatic and ethical obligations.

2.2.1 General discussion

The main concern voiced in the discussion that followed centred on being able to compare the costs of the different onchocerciasis treatment strategies. The cost of mapping needs to be assessed against the costs of MDA and TaNT.

It may be possible, with AB testing and LoaScope together, to lower the threshold that classify an area as being “at risk of SAE” from 20% mf prevalence to 5% mf prevalence, but it may not be possible to bring down the threshold to zero. Preliminary calculations that need to be refined estimate that a 5% mf prevalence of Loa would be equivalent to 20% AB prevalence. The 5% threshold is therefore in reference to the mf, not the AB. At the moment, any area with > 0% RAPLOA is being considered as a risk area, making it impossible to fund the programmes.

Focusing on high-intensity Loa prevalence is the key. Loa occurrence is often focal. There are some areas with high infection intensity, which are small areas hidden in a larger area. So, the size of implementation unit or measurement area matters. Transmission area geography has to be taken into account. It is necessary to look for areas that do not fit the geography of the rest of the district, otherwise they could be found during subsequent treatments when SAEs occur. Care must be taken not to miss small pockets, familial, geographical or otherwise. This is where SAE risk lies.

The meeting heard that there is a movement from the era of control to the era of elimination, and it is important to bear in mind the level of risk for individuals in the name of onchocerciasis elimination. In areas hypo-endemic for onchocerciasis, people who are at low risk of disease from onchocerciasis are being asked to put themselves at risk of SAEs from Loa loa.
Biometric data were gathered very effectively in Cameroon using fingerprints and electronic tablets, though the tablets were fragile. When paper records were used, many people who had been treated but not recorded were missed. Recognizing people and finding names in the paper register is difficult, and then individuals have to be retested.

It may be possible, with AB testing and LoaScope together, to lower the threshold below 5%, but it may not be possible to bring down the threshold to zero. The threshold is in reference to the mf, not the AB. Few endemic communities have < 5% mf prevalence. This is not typical. Using the current *Loa loa* endemicity estimates (available at the ESPEN [Expanded Special Project for Elimination of Neglected Tropical Diseases] portal, based on the RAPLOA), targeting for Loa mapping any area with prevalence > 5% would be a very intensive and expensive exercise, if not impossible to fund for programmes.

Focusing on high-intensity prevalence is key. *Loa* is often focal. There are some areas with high intensity, which are small areas hidden in a larger area. So, the size of implementation unit or measurement area matters. Transmission area geography has to be taken into account. It is necessary to look for areas that do not fit the geography of the rest of the district, otherwise they could be found during subsequent treatment when SAEs occur. Care must be taken not to miss small pockets, familial, geographical or otherwise. This is where SAE risk lies.
The meeting heard that there is a movement from the era of control to the era of elimination, and it is important to bear in mind the level of risk for individuals in the name of onchocerciasis elimination. In hypo-endemic areas, people who are at low risk of disease from onchocerciasis are being asked to put themselves at risk of SAEs from *Loa loa*.

Biometric data was gathered very effectively in Cameroon using fingerprints and tablets, though the tablets were fragile. When paper records were used, a lot of people who had been treated but not recorded were missed. Recognizing people and finding names in the paper register is difficult, and then individuals have to be retested.

Work is now continuing with computer scientists to improve the biometric tool so that the move away from paper records can be made for community registration during MDA and data from onchocerciasis programmes can be aligned with the existing district health information system and health system data.

### 2.2.2 Discussion on the algorithm

#### RISK-MITIGATION STRATEGIES TO ELIMINATE ONCHOCERCIASIS WHILE MINIMIZING RISK FROM *L. LOA*

1. **Onchocerciasis-endemic areas that have been previously treated**
   - **Previously treated onchocerciasis-endemic areas**
   - **Epidemiology of oncho and loiasis are known**
   - **Is *Loa* endemic?**
     - **No** (no history of SAE)
     - **Yes** (history of SAE)
   - **Scenario:**
     - **Scenario 1:** CDTI
     - **Scenario 2:** CDTI testing and untreated

   **Scenario 1a:** CDTI could proceed if it included a question regarding previous participation in MDA. All persons who had never received IVM or missed the latest round would be tested using a TaNT approach. Needs reliable records.

2. **Onchocerciasis-endemic areas not previously treated (essentially hypo-endemic areas for oncho)**
   - **If available data inconclusive: OEM by assessing presence of OV16 antibodies in DBS. Conduct RAPLOA at the same time. Store DBS to allow later assessment of *L. loa* antibodies or PCR, where relevant**
   - **Is *Loa* endemic, based on available data or elimination mapping?**
     - **No**
     - **Yes**
   - **Is *Loa* endemic, based on available data or elimination mapping?**
     - **No**
     - **Yes**
     - **Yes/low**
     - **Yes/moderate**
     - **Yes/high**
   - **Scenario**
     - **Scenario 0:** No treatment
     - **Scenario 1:** CDTI
     - **Scenario 2:** TaNT, CDTI if low *Loa* proven
     - **Scenario 3:** RAPLOA

   **Scenario 1:** L. loa is absent means RAPLOA = 0% or antibody testing = 0% in residents
   Conduct CDTI
Low risk is defined as < 5% mf prevalence.
Moderate risk is defined as ≥ 5% up to 40% mf prevalence.
High risk is defined as > 40% mf prevalence.

Good acceptance of, and agreement on, the proposed algorithm was reached. Validation in multiple settings is recommended.

The scenario of onchocerciasis-endemic areas not previously treated, and having moderate endemicity of loiasis, is particularly problematic. The factors to be weighed are the risk of delaying treatment versus the risk of SAEs.

Cameroon, the meeting heard, is a good example of working out how to operationalize this balance of risk; there are places being treated safely for Loa with low, medium and high endemic rates and places where TaNT is working. The question is how to draw that boundary well and make those programmatic decisions.

Collecting more data will be critical.

### 2.3 Revising the target threshold for stopping MDA

#### 2.3.1 CDC operational research protocol on stop MDA threshold

Programmes have to demonstrate that the upper limit of the 95% confidence interval around the estimate seroprevalence of Ov16 antibody is < 0.1% before stopping MDA. This threshold is exceedingly difficult to measure. Meeting the threshold could be a barrier to success, the meeting heard, delaying stopping, delaying post-treatment surveillance, adding cost and holding programmes back.

Work done in the United Republic of Tanzania suggests that there may be other ways to look at stopping MDA and that a higher threshold may be reasonable. That study, however, was aiming to assess different testing modalities and was not powered for stopping decisions. Some 15 years of good MDA, it was stated, ties in with a flat line pattern of seroprevalence, and it was suggested that looking at additional age groups would also be beneficial.

In areas where no infective flies or where no flies were found, seroprevalence in children aged 5–9 ranged from 0.02% to 1.3% (by ELISA). It was then stated that modelling suggests that:

- a 1% seroprevalence threshold is consistent with elimination in 99% of scenarios; and
- a 2% seroprevalence threshold is consistent with elimination in 95% of scenarios.

Modelling suggests also that thresholds may vary by baseline endemicity, with high endemicity equating to a theoretically lower threshold for elimination on the models.

Recommendation: OTS recommended OR to evaluate higher stopping thresholds.

The CDC research protocol includes the following key provisions to be tested:

- Evaluation with serology and entomology
- Stopping MDA if seroprevalences of > 0.1% and ≤ 2% and entomology meet the WHO stopping criteria
- Follow-up with targeted serology and targeted entomology annually
- After 3 years, if results continue to be consistent with interruption of transmission, repeat full serological and entomological surveys
First year (CDC protocol):

- Probability proportional to estimate size sampling of villages stratified by first-line village versus other village in transmission area for the calculation of seroprevalence
  - One first-line village per breeding site is also sampled, though the results are not included in the calculation of seroprevalence
- 2000 children in the 5–9-year age category are sampled
- Entomology performed for the entire transmission season
  - Powered to differentiate 1% for 2%
- Two collections per site weekly
- Testing: Ov16 serology by ELISA and by RDT from DBS and O-150 PCR of blackfly heads
- Added on testing of 200 people in the following age groups:
  - 1–4 years,
  - 10–14 years and
  - > 20 years.

Follow-up plans (CDC protocol):

- Protocol still in development
- Entomology: plan limited captures during the peak 1–2 months from the previous year’s catch
- Serology: plan to sample around 500 children either in the same first-line villages every year or different first-line/next to first-line villages each year
- Positive entomological signal would require investigation or restart MDA
- If no entomological signal over the 3-year period will proceed with full evaluation
- Limited baseline serologic data prior to study implementation
- Funding/time constraints make it difficult to pre-screen study sites with a pre-stop MDA survey
- But data collected during the study should allow us to look at this retrospectively
- Limited baseline entomological data make study timeline challenging.

Next steps:

- Will hear from collaborating programmes about their study sites
- Need to identify potential new sites
- Would appreciate input on data that should be collect as part of the baseline studies
- Would appreciate input on how the follow-up studies should be structured.

2.3.2 Draft TFGH operational research protocol on stop MDA threshold

The primary objectives of the operational research are:

- to provide evidence to determine the serological prevalence threshold that is consistent with elimination of onchocerciasis transmission in previously endemic areas that have completed at least the recommended number of rounds of MDA.

Secondary objectives:

- to determine which age group is ideal for measuring this threshold;
to generate blood specimens that can be used to validate new diagnostic tests and understand the relative performance of new and existing diagnostic tests; and

to generate empirical data to inform and validate transmission models.

This protocol, the meeting heard, is not meant to be a pilot study of a stop MDA survey design. Instead, it is intended to inform a revised stop MDA serological threshold.

The criteria for site selection and evaluation unit inclusion were outlined as follows:

- For an evaluation unit to be included in the study, it must have completed the recommended rounds of MDA and the programme must consider that it is ready for a stop MDA survey.
- If an entomological survey has been done, the unit should have met entomological threshold for stopping MDA.
- If a serological survey has been done, an overall seroprevalence of Ov16 antibody in children aged < 10 years with an upper 95% confidence interval of 0.1–2% would be ideal.
- The programme must also be willing to stop MDA for the length of the study unless compelling evidence surfaces that it would be necessary to restart.

An evaluation unit is defined in this context as the unit at which a stop MDA decision will be made. This is decided by the national neglected tropical diseases programme.

This protocol focuses on a longitudinal study to be conducted in 3–5 first-line villages where ongoing or recrudescent transmission is most likely to occur.

A number of factors will be taken into account in village selection, including proximity to known breeding sites, baseline prevalence, survey data, treatment history and geospatial statistics (modelling).

As a longitudinal study the same villages will be sampled every year.

In terms of study design, the meeting heard, this is a shorter protocol than the CDC protocol. To know whether it is safe to stop MDA, a cluster survey of 1600 children aged 5–9 years will be conducted at baseline 0 and at 24 months. Longitudinal data – census sampling – will be obtained from children in all study villages at 0, 12 and 24 months. Age comparison census sampling of all ages 10+ in a subset of study villages will also be conducted. Fly infectivity sampling of blackflies at the nearest breeding site to each study village will be conducted at all three time points. The study can be halted at any point if there is evidence that transmission is ongoing.

The study’s methods are to include the following:

- Human landing collection will be the primary fly collection method; traps may be included for comparison.
- Flies will be tested with the new standardized qPCR protocol.
- Participants will provide two wheels of DBS, skin snips, and urine samples.
- Skin snips will be tested with PCR; DBS will be tested with Ov16 RDT.
- DBS and urine samples will be stored for additional testing.

The study’s analysis will focus on threshold (test-specific) assessments, asking some key questions, such as:

- In a post-treatment setting, what measurable serological threshold, in which age group, is consistent with interruption of transmission?
- How do antibody levels change over time at the individual and community levels?
- How will data be generated to validate geostatistical model predictors?
2.3.3 Onchocerciasis stop MDA threshold study, United Republic of Tanzania

Dr Akili Kalinga shared experiences with meeting participants from an onchocerciasis stopping MDA study in the United Republic of Tanzania.

This study is evaluating whether MDA can be safely stopped at a serological threshold higher than that currently recommended by WHO. It is also seeking to determine Ov16 antibody seroprevalence by ELISA among children aged 5–9 years at baseline and at conclusion of the study. It is also conducting annual serological evaluations to detect any recrudescence in the study area after stopping MDA in the time period between baseline and conclusion studies and is attempting to determine baseline, interim and final seroprevalence of Ov16 by RDT.

The study has one side objective: to conduct rapid surveillance for scabies infestation before and after ivermectin MDA has been stopped.

A threshold of 2% may lead to some advantages, namely that money and resources are saved if MDA is stopped, that scarce resources can be used specifically for problem areas and that data can be used to evaluate diagnostic tests.

The study entails enrolling and consenting persons with onchocerciasis, collecting basic information about them, conducting skin examinations for onchocerciasis and scabies, collecting blood for DBS, sharing of summary results with participating communities and study of blackflies.

The laboratory in Tanga is conducting analysis of samples under the guidance of CDC, including Ov16 ELISA testing, Ov16 RDT testing and PCR testing of blackflies.

2.3.4 MDA history of study sites

Dr Laston Sitima presented the proposed study sites – two eligible districts in savannah settings: Neno and Thyolo. Both have seen uninterrupted MDA since 1997, with 100% geographical coverage and more than 80% therapeutic coverage.

The study was proposed for these two districts because entomological results from 2017 showed that most of the sites in Thyolo district passed the threshold for stopping treatment, as was the case for samples collected in 2020 in Neno district. In 2017, pool screening results from blackflies in Thyolo showed very low positivity, with only one district showing any positives. In 2020, Neno passed the threshold too. Samples were collected through human landing capture.

2.3.5 Questions and discussion

The meeting heard that there is something fundamentally different about hypo-endemic areas that sustain low level transmission over long periods of time. Elimination in these settings may require different thresholds and methods. Modelling suggests a higher threshold may be applicable in these areas.

It was recommended that parity rates be looked at as well as total fly numbers. Often transmission is maximal after peak fly densities, because there is a larger proportion of older flies that are parous. Exclusion of those aged under one year old was queried, the reason being that young infants cannot have been exposed for sufficient time to develop infection. Children under one can only have been exposed to one breeding season, and it takes up to 18 months for a mature infection to establish.
Definitions of first-line villages were sought for the CDC protocol. The meeting was given clarification that villages closest to the breeding site were chosen, often on the same side of the river and often within five kilometres. It was agreed that a more complex stratification of villages could be helpful in defining which will be included.

The stopping threshold will be based on the average seroprevalence in the area, calculated from prevalence measured in selected first-line and other villages. There is a need to look at the average but also to pay attention to signals in individual villages, to work out whether to adapt the methodology.

Collecting data from first-line villages at the time of carrying out the survey, the meeting was told, could help determine what a pre-stop survey would look like. Ideally, a pre-stop survey would be conducted for every site before launching the full study but this would mean delay and additional cost.

The draft TFGH protocol states that areas that have completed the recommended rounds of MDA and are ready for a stop MDA survey will be selected. This number is highly dependent on baseline endemicity and other factors; therefore, a rephrasing of “recommended rounds” was suggested. This terminology references the 12–15 rounds of MDA required to outlast adult female worm lifespan, but it may be updated.

A question was asked as to whether substantial changes in Ov16 seroprevalence from one year to the next were expected and whether skin-snip PCR in positive children should also be considered. This was acknowledged as a challenging issue.

The meeting was told that once purposive sampling had begun, it was not possible to calculate the 95% confidence interval currently required by the guidelines. Stratifying by first-line villages versus non-first-line, and including one first-line village for every breeding site to adapt for that ecology, might be beneficial in this respect. The intention, the meeting heard, was to come up with a standard design that builds in more redundancy around confidence intervals. In an ideal world, participants were told, conducting pre-stop surveys would allow more flexibility in the design of the second survey.
3. Consideration of next steps for moxidectin for onchocerciasis elimination

The meeting heard that the present OTS had been asked by WHO to:
- comment on proposed moxidectin implementation pilot projects;
- suggest other preparatory activities that might be needed for inclusion of moxidectin in WHO guidelines;
- consider newly identified hypo-endemic areas; and
- consider areas or populations where achieving twice per year MDA is difficult.

3.1 Data and regulatory status to date and ongoing studies

Dr Sally Kinrade provided a short recap of the current regulatory status and key data for moxidectin as well as ongoing data generation in clinical studies. (The briefing document provided to OTS members ahead of the meeting is available in Annex 2.)

Overview of clinical and non-clinical studies that formed the basis for the 2018 approval of moxidectin for treatment of onchocerciasis in ≥12 year old individuals by the FDA (and will contribute to consideration for an indication for younger children):
The meeting heard that three studies are ongoing to: (i) identify a moxidectin dose for children aged 4–11 years; (ii) compare the efficacy and safety of three annual or five biannual treatments with moxidectin or ivermectin; and (iii) to increase the database on the safety of a single dose of moxidectin in individuals with and without detectable levels of skin microfilariae (n=10000) compared to ivermectin (n=2500). A study on safety in Loa loa is also in preparation.

3.2 Pilot implementation studies of moxidectin for onchocerciasis under discussion

Dr Charles MacKenzie expanded the information provided in the briefing document on the two moxidectin pilot implementation projects being discussed by national programmes with support from the End Fund.

One project is planned to take place on the Senegal–Mali border in areas which are among the last areas in these two countries where transmission still occurs. Successful elimination of transmission in these areas is crucial to nationwide elimination of O. volvulus transmission. In the target population in these areas (around 60 000–70 000 people in Senegal and 220 000–250 000 people in Mali) it is hard to achieve adequate, sustained exposure to ivermectin due to two factors: the endemic areas cross national borders and the target populations, commonly gold miners or farmers, are highly mobile, resulting in a variable history of ivermectin treatment and exposure to infective vectors.

The second project being discussed would take place in Ethiopia in two newly discovered hypo-endemic areas (overall population 60 000–70,000) which have never received any MDA. Important components being addressed include obtaining national approval, understanding the social situation, using spatial intelligence to map the location of populations in detail and preparing protocols. The protocols will be informed by and similar to those used during the first community studies of ivermectin. High coverage is central, as is understanding of reasons for non-compliance and the acceptability of moxidectin. Evaluation of the acceptability of treatment with moxidectin could not be included in the protocols of the previous and ongoing studies because these are double-blinded. Assessments will include vector infectivity and skin microfilariae levels at baseline, then at 2 and 4 years.

3.3 Questions and discussion

Comment was requested on the nature of the SAEs observed after moxidectin and ivermectin treatment given the high proportion of individuals with SAEs (39/978 (4%) with moxidectin and 18/494 (3.6%) with ivermectin). The meeting was told that in this study all people were followed for all events for 18 months, and these SAEs were recorded over the first 6 months after treatment, not just during the immediate follow-up period. None of the SAEs were related to moxidectin or ivermectin treatment.

Moxidectin was approved by the FDA in 2018 for treatment of ≥ 12 year old individuals with onchocerciasis. The FDA is recognized by WHO as a “stringent regulatory authority” (SRA). Therefore, WHO prequalification can be based on an abbreviated process designed by WHO for SRA-approved products.\(^1\) Discussion is already under way with the WHO prequalification department.

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\(^1\) For more information, see WHO SRA-approved multisource (generic) or innovator finished pharmaceutical products (6).
For the Senegal–Mali border study, the expectation is that there will be skin snips and entomological follow up. The project’s first step will be a social assessment to understand the area better before any new tools are introduced. Until a moxidectin dose for children and sufficient safety data become available, the implementation project would give ivermectin to those aged 5–11 years and moxidectin to those aged at least 12. The challenge will be in explaining why this is the case. A paediatric dose is due to be selected in the second half of 2022.

OTS members agreed with the thinking behind these moxidectin implementation studies and indicated that these respond to the required actions relating to moxidectin in the road map and could help move forward the objectives stated therein. It was noted that the cross-border study would need to ensure that the treatment coverage achieved is well documented during each treatment round and that reasons for refusal (including assumptions about the medicine) are identified.

Medicines Development for Global Health confirmed that it is willing to support any projects that will evaluate the utility of moxidectin, including for other use cases.

WHO should review the available evidence and provide a recommendation on the programmatic use of moxidectin. Use of moxidectin for MDA will be challenging until approval for paediatric use.
4. Development of a dossier for verification of onchocerciasis elimination

4.1 Ecuador verification dossier

The meeting then heard about the various components of the Ecuador verification dossier and general approach.

There are two components in preparing the document for verification, namely the gathering and tabulation of all data recommended by WHO, followed by writing of the document.

Data gathering is a very laborious process, the meeting heard. A WHO guidance document came out in 2001 and there is now an update to this document.

Following this process, the next step consists of creating a national committee of onchocerciasis experts, to determine what data to include in the report in order to meet WHO guidelines. The committee also assist in reviewing data – compiling all scientific and public documents – and this is the source of most data. Any internal MoH documents related to onchocerciasis, and all onchocerciasis control programme documents and records also require review, which makes this a huge assignment requiring many months to complete. Publishing results in peer-reviewed journals is also of huge benefit in writing the dossier, the meeting heard, and adds credibility when the dossier is subsequently reviewed by WHO.

Data needs to start with mapping, and should include all entomology and ophthalmology studies.

Pre and post treatment studies from sentinel communities are needed that will be used to show the impact of treatment. Post endemic surveillance studies should also be included.

The meeting then heard the essential components for writing the document, which include descriptions, methodologies and assessments of the various criteria used for evaluation of decisions to stop MDA and PTS studies.

4.2 Dossier preparation in the African Region

Dr Didier Bakajika then outlined the considerations for African programmes in developing a dossier for verification of onchocerciasis elimination, focussing particularly on key sections of the dossier.

Dossiers will typically include information about the parasite, including the history of onchocerciasis in the country and a description of co-endemicity with Loa loa. They will also include basics about the parasite, the vector(s) of transmission and their distribution in the country and a general epidemiology of onchocerciasis including information about geographical distribution, transmission foci, known information about clinical manifestations of onchocerciasis, descriptions of any co-endemicity with loiasis and consideration of particular populations (for example nomadic or mobile populations). There will also be a description of any interventions carried out against onchocerciasis prior to the launch of the current programme.
Further background in the elimination dossier will describe national programme goals, objectives and date of establishment. It will also give a history of the programme’s activities from start to finish, describe the national elimination plan, the structure of the onchocerciasis programme, implementation of MDA and supervision.

Management and monitoring of SAEs after MDA with ivermectin (as well as moxidectin) will also be covered, alongside descriptions of the national onchocerciasis elimination committee structure, a description of challenges faced and any studies performed to develop evidence to overcome these challenges.

The second section of the dossier concentrates, the meeting heard, on the delineation of endemicity. This includes data used to classify implementation units as endemic and non-endemic, methods/protocols used for mapping, maps of the endemicity of onchocerciasis as well as loiasis mapping (including validation, roll out of RAPLOA and any additional loiasis surveys). This section is also to include information about the regional context, the occurrence of onchocerciasis and the current status of onchocerciasis elimination in neighbouring countries.

Section 3 of an elimination dossier requires information about the interventions carried out for the interruption of transmission, to include complete information about all aspects of MDA, as well as vector control interventions.

A section is also required, the meeting heard, on any special issues that could have affected onchocerciasis activities (such as migration or security or political issues, for example).

The meeting heard that the Onchocerciasis Elimination Dossier template consists in total of eight sections:

- Introduction
- Population
- Mapping
- MDA
- Monitoring and evaluation
- Stop MDA
- Surveillance
- Additional comments

Next steps, the meeting was told, currently include the organization of a small working group to develop the dossier as a tool (December 2021), the setting up of a working session to go through the dossier to understand all parameters and set a logic for programming, and consideration of the programming stage (Q1/2022). After this, the tool is to be shared with stakeholders and onchocerciasis experts for review and feedback (Q1/2022) before it is presented during the next OTS meeting (2022) and disseminated at the end of the year.

The meeting was reminded that ongoing preparation is key and that it is not necessary to have achieved elimination to start thinking about the dossier.

4.3 Questions and discussion

In the discussion following these presentations, the final discussion of the meeting, a question was raised about post-transmission surveillance in Ecuador, and whether it was necessary to take into account different vector species and different time horizons for vector species. Questions of indicators of environmental change might also have helped interrupt transmission, alongside ivermectin. The response stated that there was only one efficient vector species in the country and that that species was fortunately concentrated in one area.
In response to a question about whether WHO planned to revisit milestones and targets in the road map given the impact of COVID-19, the meeting was told that there was no intention to do so, given that one MDA missed would not have a severe impact in the longer term.

Concerns were expressed about the length of the process for preparing dossiers. The meeting was told that WHO will provide support and technical assistance where needed.

Finally, meeting participants were reminded of two considerations when preparing dossiers, namely that it is best to work on the dossier as the process is being carried out, particularly with respect to documenting methodology, and also that entire countries are evaluated for elimination, not only the known transmission areas.
5. Meeting closure

Following the final deliberations and discussions, the fifth meeting of the OTS was brought to a close. Members and presenters were thanked for their time and participation, and the meeting was adjourned.
References


Annex 1. List of participants

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Annex 2. Briefing document on moxidectin and pilot implementation studies for onchocerciasis elimination
Onchocerciasis Technical Advisory Subgroup (OTS)

Meeting December 2021

Briefing document

Moxidectin for onchocerciasis elimination

Agenda item:

3. Consideration of next steps for moxidectin for onchocerciasis elimination:

Does the OTS support country ‘Pilot moxidectin implementation projects’ to move towards collection of data on moxidectin effectiveness and safety in programmatic settings as requested in the WHO NTD roadmap 2021-2030?

OTS members are requested to ask for any additional information or clarification they would like to receive prior to the meeting.
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Figure 12: OCRC CTC Severity of for different clinical Mazzotti reactions across all and by range of pre-treatment skin mf density after treatment with 8 mg moxidectin or 150 µg/kg ivermectin (adapted from [2] supplementary appendix)

Figure 13: OCRC CTC Severity of for different laboratory Mazzotti reactions across all and by range of pre-treatment skin mf density after treatment with 8 mg moxidectin or 150 µg/kg ivermectin (adapted from [2] supplementary appendix)

Figure 14: OCRC CTC Severity of for different ocular Mazzotti reactions across all and by range of pre-treatment skin mf density after treatment with 8 mg moxidectin or 150 µg/kg ivermectin (adapted from [2] supplementary appendix)

Figure 15: Percentage of participants by post-treatment time period for resolution of their Mazzotti reactions

Figure 16: Cumulative percentage of participants with clinical Mazzotti reactions (A, B) and ocular Mazzotti reactions (C, D) by day after treatment the reaction started (A,C) and resolved (B,D)

4.4 Overview of information included in the New Drug Application to the US FDA

Figure 17: Selected statistics on elements included in the NDA to the US FDA and US FDA review times and outputs

4.5 Graphic presentation of design of ongoing studies of moxidectin for onchocerciasis

Figure 18: Design of Pediatric dose finding study (MDGH-MOX-1006)

Figure 19: Design of repeat dose efficacy and safety study (MDGH-MOX-3001)

Figure 20: Design of single dose safety study (MDGH-MOX-3002)

5 References
1 Development and data on moxidectin to date

1.1 History of development of moxidectin for onchocerciasis control and elimination

Development of moxidectin as a potential new drug for onchocerciasis control and elimination was initiated by WHO/TDR. It was initially conducted in collaboration with the owner of moxidectin at the time, Wyeth and its veterinary ‘arm’ Fort Dodge Animal Health (FDAH). Following take-over of Wyeth by Pfizer, Pfizer withdrew from the collaboration agreement with WHO and TDR completed the Phase 3 study on its own, following guidance from TDR and APOC External Advisory Committees.

In 2014, WHO licensed all data on moxidectin at its disposal (acquired in the Phase 2 and Phase 3 studies managed and financed by TDR, as well as data from clinical and preclinical studies provided to WHO as per legal agreements with Wyeth and later Pfizer) to Medicines Development for Global Health (MDGH).

For further details on the development history see Supplementary Information section 4.1.

MDGH is an Australian non-profit biopharmaceutical company (https://www.medicinesdevelopment.com/) dedicated to the development and delivery of affordable medicines for diseases of poverty. For further information on MDGH see Supplemental Information section 4.2.

MDGH completed all further activities and studies required to support a New Drug Application (NDA) to the US Food and Drug Administration (US FDA), including establishment of moxidectin tablet manufacturing.

1.2 Overview of non-clinical and clinical studies conducted to date

Figure 1 provides an overview of the non-clinical pharmacology, pharmacokinetic, toxicokinetic and toxicology as well as the clinical studies completed to date. All clinical studies completed to date were single dose studies.

Figure 1: Overview of non-clinical and clinical studies

1.3 Efficacy data

The effect of a single dose of moxidectin compared to ivermectin on skin microfilariae levels to 18 months was evaluated in the Phase II study in Ghana (River Tordzi basin) and the Phase III study in Ghana (Nkwanta district), Liberia, DRC.

The efficacy data after an 8 mg dose of moxidectin was consistent across both studies [1,2].
Figure 2 shows the skin microfilariae (mf) densities for each Phase III study participant. The same difference in the pattern of initial skin mf decreases between moxidectin and ivermectin and subsequent increases was observed in the Phase II study. The Phase II study, which included more frequent skin mf density evaluations than the Phase III study, furthermore showed that skin mf decreased more rapidly after moxidectin than after ivermectin treatment (see Supplemental Information, Figure 8).

Figure 3 shows the geometric mean skin mf densities [A] and percentage of participants with undetectable skin mf densities [B] at each follow up time point. At the primary efficacy endpoint 12 months after treatment, skin mf density was significantly lower after moxidectin (adjusted geometric mean 0·6 [95% CI 0·3–1·0]) than after ivermectin (4·5 [3·5–5·9]; difference 3·9 [3·2–4·9], p<0·0001; treatment difference 86%). The differences in skin mf densities were also statistically significant at month 1, 6 and 18 (p<0.0001, [2]). Details of the statistical analyses are provided in [2] and its supplementary information.

![Figure 2: Skin microfilariae densities 1, 6, 12 and 18 months after a single 8 mg dose of moxidectin or the standard dose of ivermectin relative to pre-treatment density for each participant in the Phase III study (adapted from [2])]
A B

Figure 3: A) Geometric mean (95% CI) of skin microfilariae densities after a single 8 mg dose of moxidectin or the standard dose of ivermectin, B) percentage of participants with undetectable skin mf levels at each follow up time point in the Phase III study (adapted from [2])

Figure 4 presents the same data summarized to show the percentage of participants with ‘Sustained Microfilariae Reduction’: with undetectable skin mf densities at Months 1 and 6 and at Months 1, 6 and 12 for all participants (A) and by range of pre-treatment densities (B and C).

A B C

Figure 4: Percentage of participants in the Phase III study with undetectable skin microfilariae levels after a single dose of 8 mg moxidectin or the standard dose of ivermectin, A) at Month 1 and 6 and at Month 1, 6 and 12 after treatment across all pre-treatment skin mf densities, B) at Month 1 and 6 by pre-treatment skin mf density (mf/mg skin), C) at Month 1, 6 and 12 by pre-treatment skin mf density mf/mg skin.

1.4 Clinical safety data

The Supplementary Information includes details on the terminology used (section 4.3.2), the adverse event severity grading (section 4.3.3) and laboratory evaluations conducted (section 4.3.4).
1.4.1 Adverse events in uninfected individuals

Across the six Phase I studies in 259 healthy adult men and women receiving placebo or moxidectin at different dose levels, 48.3% of participants reported at least one adverse event (AE) with 41/259 (15.8%) reporting AEs considered by the investigator as possibly treatment related.

The adverse event profile:

- was similar in moxidectin treated healthy volunteers and placebo treated volunteers
- did not show an increase in frequency or severity of AEs with increasing moxidectin dose
- did not indicate dose-limiting adverse events
- did not include serious adverse events (SAEs)
- did not include changes in laboratory parameters.

For further information see Supplemental Information section 4.3.5 and references [3–8].

1.4.2 Adverse events in *O. volvulus* infected individuals

Details of the safety evaluations and their timing are provided in Supplemental Information section 4.3.9.

### Table 1: Overview of adverse events reported in the Phase II and Phase III study with relationship to treatment as assessed by each individual investigator

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Phase II MOX (8 mg) n = 38 n (%)</th>
<th>Phase II IVM (150 µg/kg) n = 45 n (%)</th>
<th>Phase III MOX (8 mg) n = 978 n (%)</th>
<th>Phase III IVM (150 µg/kg) n = 494 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To month 18</td>
<td>To Day 180 post treatment (app. 5 half lives of moxidectin)</td>
<td>After Day 180 to Month 12 or 18</td>
<td></td>
</tr>
<tr>
<td>At least 1 AE*</td>
<td>37 (97.4)</td>
<td>45 (100)</td>
<td>978 (100)</td>
<td>491 (99.4)</td>
</tr>
<tr>
<td>Mazzotti reaction</td>
<td>37 (97.4)</td>
<td>43 (95.6)</td>
<td>966 (98.8)</td>
<td>480 (97.2)</td>
</tr>
<tr>
<td>ADR**</td>
<td>2 (5.3)</td>
<td>2 (4.4)</td>
<td>25 (2.6)</td>
<td>13 (2.6)</td>
</tr>
<tr>
<td>Ocular AEs***</td>
<td>2 (5.3)</td>
<td>1 (2.2)</td>
<td>205 (21.0)</td>
<td>79 (16.0)</td>
</tr>
<tr>
<td>Total SAE*</td>
<td>2 (5.3)</td>
<td>0</td>
<td>39 (4.0)</td>
<td>18 (3.6)</td>
</tr>
<tr>
<td>requiring hospitalization</td>
<td>2 (5.3)</td>
<td>0</td>
<td>32 (3.3)</td>
<td>17 (3.4)</td>
</tr>
<tr>
<td>leading to withdrawal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>leading to death</td>
<td>0</td>
<td>2</td>
<td>2 (0.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>considered ADR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>At least 1 AE*</td>
<td>698 (71.4)</td>
<td>352 (71.3)</td>
<td>39 (4.0)</td>
<td>18 (3.6)</td>
</tr>
<tr>
<td>Mazzotti*</td>
<td></td>
<td></td>
<td>63 (6.4)</td>
<td>44 (8.9)</td>
</tr>
<tr>
<td>ADR**</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Ocular AEs*</td>
<td>39 (4.0)</td>
<td>18 (3.6)</td>
<td>32 (3.3)</td>
<td>17 (3.4)</td>
</tr>
<tr>
<td>Total SAE*</td>
<td></td>
<td></td>
<td>9 (0.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>requiring hospitalization</td>
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<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>leading to withdrawal</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>leading to death</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>considered ADR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All events, including events considered not related to treatment, Mazzotti reactions (i.e. related to the immunological response of the body to dead and dying microfilariae) or related to treatment but not as a Mazzotti reaction

** ADR: Adverse Drug Reactions (AEs assessed as related to treatment but not as a Mazzotti reaction

*** includes both Mazzotti and non-Mazzotti ocular events

Differences to [2] are due to Opoku et al. reporting AE characterization based on central expert review rather than individual investigator assessment (see section 4.3.8).
Table 2: Mazzotti reactions and Adverse Drug Reactions Occurring in > 10% of Moxidectin and Ivermectin-treated Participants in Phase III

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Moxidectin N = 978</th>
<th>Ivermectin N = 494</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>721 (74)</td>
<td>390 (79)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>640 (65)</td>
<td>268 (54)</td>
</tr>
<tr>
<td>Musculoskeletal pain(^a)</td>
<td>623 (64)</td>
<td>257 (52)</td>
</tr>
<tr>
<td>Headache</td>
<td>566 (56)</td>
<td>267 (54)</td>
</tr>
<tr>
<td>Lymphocytopenia(^*)</td>
<td>470 (48)</td>
<td>215 (44)</td>
</tr>
<tr>
<td>Tachycardia(^b)</td>
<td>382 (39)</td>
<td>148 (30)</td>
</tr>
<tr>
<td>Orthostatic tachycardia(^c)</td>
<td>333 (34)</td>
<td>130 (26)</td>
</tr>
<tr>
<td>Non-orthostatic tachycardia(^d)</td>
<td>179 (18)</td>
<td>57 (12)</td>
</tr>
<tr>
<td>Rash(^e)</td>
<td>358 (37)</td>
<td>103 (21)</td>
</tr>
<tr>
<td>Abdominal pain(^f)</td>
<td>305 (31)</td>
<td>173 (35)</td>
</tr>
<tr>
<td>Hypotension(^g)</td>
<td>289 (30)</td>
<td>125 (25)</td>
</tr>
<tr>
<td>Orthostatic hypotension(^h)</td>
<td>212 (22)</td>
<td>81 (16)</td>
</tr>
<tr>
<td>Pyrexia/Chills</td>
<td>268 (27)</td>
<td>88 (18)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>240 (25)</td>
<td>125 (25)</td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>226 (23)</td>
<td>102 (21)</td>
</tr>
<tr>
<td>Neutropenia(^**)</td>
<td>197 (20)</td>
<td>112 (23)</td>
</tr>
<tr>
<td>Cough</td>
<td>168 (17)</td>
<td>88 (18)</td>
</tr>
<tr>
<td>Lymph node pain</td>
<td>129 (13)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>121 (12)</td>
<td>44 (9)</td>
</tr>
<tr>
<td>Diarrhea/Gastroenteritis/Enteritis</td>
<td>144 (15)</td>
<td>84 (17)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>112 (12)</td>
<td>65 (13)</td>
</tr>
<tr>
<td>Peripheral swelling</td>
<td>107 (11)</td>
<td>30 (6)</td>
</tr>
</tbody>
</table>

\(^a\)Includes “myalgia”, “arthralgia”, “musculoskeletal pain”, “pain” and “back pain”; \(^b\)Includes “orthostatic heart rate increased”, “postural orthostatic tachycardia syndrome”, “heart rate increased” and “sinus tachycardia”; \(^c\)Includes “orthostatic heart rate increased” and “postural orthostatic tachycardia syndrome”; \(^d\)Includes “heart rate increased”, “tachycardia”, and “sinus tachycardia”; \(^e\)Includes “rash,” “papular rash” and “urticaria”; \(^f\)Includes “abdominal pain”, “abdominal pain upper” and “abdominal pain lower”; \(^g\)Includes “orthostatic hypotension”, “blood pressure orthostatic decreased”, “blood pressure decreased”, “mean arterial pressure decreased”, “hypotension”; \(^h\)Includes “orthostatic hypotension”, and “blood pressure orthostatic decreased”.

**Neutropenia is defined as absolute neutrophil count less than 1 x 10\(^9\)/L.**

Table 3: Ocular Mazzotti Reactions and Adverse Drug Reactions as assessed by each investigator Occurring in > 0.5% Moxidectin-treated Participants

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Moxidectin N = 978</th>
<th>Ivermectin N = 494</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>78 (8)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>64 (7)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>Visual impairment(^*)</td>
<td>25 (3)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>21 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Conjunctivitis allergic</td>
<td>19 (2)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Ocular discomfort(^**)</td>
<td>18 (2)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Ocular and conjunctival hyperemia</td>
<td>17 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>13 (1)</td>
<td>10 (2)</td>
</tr>
</tbody>
</table>

\(^*\)Includes “visual impairment”, “blurred vision” and “low vision acuity”

\(^**\)Includes “foreign body sensation”, “ocular discomfort” and “abnormal sensation in the eye”

Further data are provided in Supplementary Information section 4.3.11.

### 1.5 US Food and Drug Administration approval

MDGH submitted a New Drug Application (NDA) to the US Food and Drug Administration (US FDA) on 13 October 2017 (NDA210867). The US FDA accepted it for priority review on 13 December 2017. On 13 June 2018, the US FDA approved moxidectin for treatment of onchocerciasis in individuals at least 12 years old. On 5 March 2021, the US FDA approved
NDA 210867 supplement 003, which included the addition of the data from a rat pre-post natal study conducted by currently required methods and resulted in updated prescribing information. ‘Selected statistics’ on elements included in the NDA are provided in Supplemental Information section 4.4. The US FDA approved labelling (package insert) is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varAppNo=210867.

2 Ongoing activities for moxidectin for onchocerciasis

2.1 Ongoing studies

Three studies are currently ongoing (Table 4) designed to provide data required for decisions on inclusion of moxidectin in WHO guidelines and country policies. The protocols are available at https://mox4oncho-multimox.net/. Further information on study design is provided in Supplemental Information section 4.5.

Funding for these studies is coming from MDGH and EDCTP (https://www.edctp.org/projects-2/edctp2-projects/targeting-control-and-elimination-of-nids-through-clinical-trials-2017/).

Additional funding is required to accelerate completion of studies 3001 and 3002 and is being sought.

Table 4: Ongoing studies of moxidectin for onchocerciasis

<table>
<thead>
<tr>
<th>Short title (ID)</th>
<th>[Clinical Trial Registry] Location</th>
<th>Study characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric dose finding study (MDGH-Mox-1006) [NCT03962062, PACTR201907566746388] Nkwanta District, Oti region, Ghana</td>
<td>Design: Prospective, age-stratified, adaptive, open-label, single-dose pharmacokinetic and safety study of moxidectin in children and adolescents aged 4 to 17 years with, or at risk of, infection with O. volvulus. Dose recommendations are expected 4Q 2022 – 1Q 2023.</td>
<td></td>
</tr>
<tr>
<td>Multi-dose efficacy and safety study (MDGH-Mox-3001) [NCT03876262, PACTR202004639229710] Ituri, DRC</td>
<td>Design: Double blind randomized study comparing the efficacy and safety of three annual and five biannual treatments with 8 mg moxidectin or 150 µg/kg ivermectin in male and female individuals aged ≥12 years infected with O. volvulus. A protocol amendment is in preparation to reduce the sample size of 1000 to that needed for the primary efficacy outcome while retaining the 3:1 moxidectin : ivermectin randomization ratio (current estimate around 320 - 350).</td>
<td></td>
</tr>
<tr>
<td>Single dose safety study (MDGH-Mox-3002) [NCT04311671, PACTR202003567524647] Ituri, DRC</td>
<td>Design: Double blind randomized study comparing the safety of a single dose of 8 mg moxidectin (n=10000) and 150 µg/kg ivermectin (n=2500) in male and female individuals aged ≥12 years with or without detectable levels of O. volvulus skin microfilariae.</td>
<td></td>
</tr>
</tbody>
</table>

The ‘Institut de recherche pour le développement’ (Montpellier, France) is preparing a study to evaluate the safety of moxidectin in individuals with very low Loa loa microfilaraemia.

2.2 Development of a paediatric formulation

The size of the US FDA approved 2 mg tablet (8.0 mm x 4.5 mm x 3.0 mm) was chosen to allow swallowing by children down to 4 years old. The choice was informed by the recommendations of the Technical Consultative Committee of APOC that moxidectin development target inclusion of children down to 4 years.

In view of small 4-5 year old children possibly preferring a different formulation and in particular in view of the ongoing development of moxidectin for other diseases (e.g. scabies), development of a paediatric formulation has been initiated with funding from MDGH and...
2.3 US FDA Certificate of Pharmaceutical Product for improved manufacturing process

MDGH is finalizing submissions to the US FDA for approval of an improved manufacturing process for 2 mg moxidectin tablets. Once the US FDA has approved this, MDGH will request a new Certificate of Pharmaceutical Product to be included in all requests for import permits to confirm that the moxidectin tablets comply with Stringent Regulatory Authority quality standards.

3 Moxidectin pilot implementation projects

MDGH has been contacted by a number of organisations for provision of moxidectin for moxidectin pilot implementation projects (MPIP). Such projects could contribute to demonstration of the effectiveness and safety of moxidectin in programmatic settings, a ‘required action’ outlined in the NTD road map 2021–2030.

MDGH is willing to support such projects. They represent the next step after clinical trials informing the regulatory approval and the ongoing studies that will provide additional information to inform WHO guidelines and country policies on the appropriate use of moxidectin in programmatic settings.

While moxidectin has received regulatory approval from the US FDA, it has not yet been registered in the countries where the MPIP will be conducted. Thus, obtaining the relevant approvals for the MPIPs in each country is a prerequisite for MPIP.

MDGH has agreed to supply moxidectin tablets for pilot implementation projects conducted under appropriate country regulatory dispensation. MDGH support will furthermore provide the documentation MDGH submitted to the US FDA for regulatory approval to support approvals of MPIPs in the countries.

3.1 Projects currently under discussion between the END Fund and onchocerciasis control programmes in Senegal, Mali and Ethiopia

Overall rationale: In the proposed areas, the countries are facing specific obstacles towards elimination of transmission with ivermectin (IVM) that could be addressed through alternative treatment strategies including local vector control and initiatives to increase treatment coverage. Inclusion of moxidectin, rather than ivermectin in these strategies was decided upon because of moxidectin’s higher efficacy in reducing and sustaining reduced skin microfilariae levels.

3.1.1 Location A. Senegal/Mali

Challenge faced: In the target population it is hard to achieve adequate, sustained exposure to ivermectin due to the fact that this population is in an endemic area that crosses national borders. The population, commonly gold miners or farmers, is highly mobile and often has a variable history of IVM treatment and previous exposure to the infection.

Importance of these endemic areas: These are amongst the very last areas in these two countries where infection and transmission still occurs. Successful elimination of transmission in these areas is crucial to nationwide elimination of O. volvulus transmission.

Total Population size: Between 60,000 and 70,000 people in Senegal, between 220,000 and 250,000 people in Mali.

3.1.2 Location B. Ethiopia

Challenge faced: Two onchocerciasis hypo-endemic areas were recently identified, and thus MDA has not yet been implemented.
**Importance of these endemic areas:** Elimination of *O. volvulus* transmission in these areas as fast as possible is required for Ethiopia to achieve elimination nationwide.

**Total Population size:** Area 1 ~25,000, Area 2 ~15,000.

### 3.1.3 Anticipated field procedures

The END Fund and partners have been engaged in discussions with national onchocerciasis leaders in the three countries for over a year through seminars, in person discussions as well as Zoom presentations and discussions.

The procedures related to the use of moxidectin, will be informed and largely similar to those taken for the ivermectin ‘community studies’ undertaken with the objective to obtain large scale community-based data on the efficacy and safety of ivermectin, immediately after it had received regulatory approval in France. The specific aim will be to collect a wide range of data that can inform potential WHO guidelines and country policies for the use of moxidectin by onchocerciasis elimination programmes.

### 4 Supplemental information

#### 4.1 Timeline of moxidectin development for onchocerciasis elimination

![Figure 5: Key events in development of moxidectin for onchocerciasis elimination to US FDA regulatory approval](Image)

**4.2 Additional Information on MDGH and its portfolio**

MDGH is a social enterprise and a largely self-funded non-profit pharmaceutical company. MDGH was founded for the development of drugs for infectious and neglected diseases affecting poor and marginalized populations and which consequently have no prospects for generating profit.

MDGH has only 20 employees who work with a large network of advisers/consultants and organisations with the diverse expertise required for drug development for regulatory registration. Figure 6 shows the organisations with whom MDGH engaged for bringing moxidectin to registration with the US FDA.
MDGH is also evaluating the value of moxidectin for treatment of scabies and supporting partner sponsored studies in the treatment of soil transmitted helminths, lymphatic filariasis, Strongyloides and head lice. Data from these studies will inform future decisions on continued development of moxidectin for these indications.

MDGH has recently in-licensed from Amgen (previously from Celgene) a compound (CC-11050) for development as a potential treatment of the inflammatory effects of TB and leprosy.

Figure 7 provides an overview of MDGH’s current portfolio.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>SRA Approved</th>
<th>IIIb/IV studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxidectin</td>
<td>Onchocerciasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stringent Regulatory Authority (SRA) Approved (US FDA)</td>
<td></td>
</tr>
<tr>
<td>Scabies</td>
<td></td>
<td>Phase Ia dose finding</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Finish 24 21</td>
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</tr>
<tr>
<td>Soil Transmitted Helminths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proof of concept complete</td>
<td></td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early data soon to be published</td>
<td></td>
</tr>
<tr>
<td>Strong/loidiasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proof of Concept complete</td>
<td>Long term follow up ongoing</td>
</tr>
<tr>
<td>Head lice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC-11050 (PDE4 Inhibitor)</td>
<td>Leprosy- type 2 reaction</td>
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<td>Proof of concept complete</td>
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<tr>
<td>Tuberculosis</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Proof of concept complete</td>
<td></td>
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</table>

**Figure 7:** Overview of MDGH portfolio for development of moxidectin for onchocerciasis and other diseases and of CC-11050 for inflammatory effects of TB and leprosy
### 4.3 Additional information on clinical studies

#### 4.3.1 Doses, participant numbers and follow up duration

**Table 5: Moxidectin doses and duration of collection of adverse events in the 8 clinical studies**

<table>
<thead>
<tr>
<th>Study short title (study ID)</th>
<th>Moxidectin formulation Age, sex Dose levels - Number treated</th>
<th>Inpatient Treatment Follow-up</th>
<th>Total Follow-up</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td><strong>Healthy volunteers</strong></td>
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<td></td>
</tr>
<tr>
<td>Single ascending dose (100-EU)</td>
<td>Liquid Adult men 3 mg, n=5 9 mg, n=11 18 mg, n=5 36 mg, n=10 Placebo, n=6</td>
<td>3 days</td>
<td>84 D</td>
<td>[3]</td>
</tr>
<tr>
<td>Relative bioavailability (101-EU)</td>
<td>Adult men Liquid 10 mg, n=29 Tablet 10 mg, n=29</td>
<td>3 days</td>
<td>180 D</td>
<td>[4]</td>
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<tr>
<td>Milk excretion (1002-EU)</td>
<td>Tablet Adult women 8 mg, n=12</td>
<td>8 days</td>
<td>90 D</td>
<td>[5]</td>
</tr>
<tr>
<td>Drug interaction (1004-EU)</td>
<td>Tablet Adult, 36 men, 2 women 8 mg, n=38 (midazolam D1, moxidectin D3, midazolam D7 and D89)</td>
<td>5 days</td>
<td>93 D</td>
<td>[6]</td>
</tr>
<tr>
<td>Food effect (1005-EU)</td>
<td>Tablet Adult men 8 mg, n=54</td>
<td>3 days</td>
<td>90 D</td>
<td>[7]</td>
</tr>
<tr>
<td>Cardiac safety QT (1008)</td>
<td>Tablet Adult men 4 mg, n=10 8 mg, n=10 16 mg, n=10 24 mg, n=10 36 mg, n=10</td>
<td>3 days</td>
<td>12 W</td>
<td>[8]</td>
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<tr>
<td><strong>O. volvulus infected participants</strong></td>
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</tr>
<tr>
<td>Phase II</td>
<td>Tablet Adult men and women 2 mg, n= 44 4 mg, n=45 8 mg, n=38 Ivermectin, n=45</td>
<td>18 days</td>
<td>18 M</td>
<td>[1]</td>
</tr>
<tr>
<td>Phase III</td>
<td>Tablet ≥12 years men and women 8 mg, n=978 Ivermectin, n=494</td>
<td>6 days</td>
<td>12/18 M*</td>
<td>[2]</td>
</tr>
</tbody>
</table>

* Follow-up reduced from 12 to 18 months in Amendment 3 due to financial constraints following Pfizer withdrawal from the collaboration agreement with WHO affecting around 22% of participants.

D: day(s), W: weeks, M: months
Table 6: Dose (µg or nmol) per kg after 8 mg moxidectin and 150 µg/kg ivermectin administered with 3 mg tablets

<table>
<thead>
<tr>
<th>Participant Weight</th>
<th>Moxidectin µg/kg</th>
<th>Moxidectin nmol/kg</th>
<th>Number of 3 mg ivermectin tablets</th>
<th>Ivermectin µg/kg</th>
<th>Ivermectin nmol/kg**</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>308</td>
<td>481</td>
<td>6</td>
<td>231</td>
<td>264</td>
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<tr>
<td>44</td>
<td>182</td>
<td>284</td>
<td>6</td>
<td>136</td>
<td>156</td>
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<tr>
<td>45</td>
<td>178</td>
<td>278</td>
<td>9</td>
<td>200</td>
<td>229</td>
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<tr>
<td>64</td>
<td>125</td>
<td>195</td>
<td>9</td>
<td>141</td>
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<td>65</td>
<td>123</td>
<td>192</td>
<td>12</td>
<td>185</td>
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<tr>
<td>84</td>
<td>95</td>
<td>149</td>
<td>12</td>
<td>143</td>
<td>164</td>
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</tbody>
</table>

* Molecular weight moxidectin: 639.8, ** Molecular weight ivermectin H2B1a 875.1, ivermectin H2B1b 861.07 – calculation of nmol/kg assumes 90% H2B1a as per US FDA Summary Basis of Approval 1996

4.3.2 Clinical safety data terminology

Table 7: Terminology for characterizing adverse events

<table>
<thead>
<tr>
<th>Term</th>
<th>Abbr.</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>AE</td>
<td>Any untoward medical occurrence after treatment, i.e. any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the treatment</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>ADR</td>
<td>Adverse event considered possibly, probably or definitely caused by the drug but not considered a Mazzotti reaction. Investigators characterized each adverse event as ‘adverse drug reaction’ (Phase I, II and III) or Mazzotti reaction (Phase II, and III) while blinded to the treatment.</td>
</tr>
<tr>
<td>Laboratory event</td>
<td>-</td>
<td>Any change in hematological, serum biochemistry or urinalysis values that was considered clinically significant by the investigator or met pre-defined criteria for absolute levels or changes from pre-treatment values.</td>
</tr>
<tr>
<td>Mazzotti reaction</td>
<td>MAZ</td>
<td>Signs and symptoms of the immunological response of the body to dead and dying microfilariae. These represent the signs and symptoms of onchocerciasis and can increase in severity or appear after administration of a drug resulting in accelerated death of microfilariae (such as ivermectin, diethylcarbamazine, moxidectin). Given that appearance of Mazzotti reactions after treatment or increasing severity of a Mazzotti reaction present before treatment is due to the effect of the drug on the microfilariae, such reactions are by definition ‘treatment related’, i.e. drug reactions. Because these Mazzotti reactions are the consequence of a desired drug effect, data analysis separates Mazzotti reactions from ‘adverse drug reactions’</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>SAE</td>
<td>Any adverse event which Results in death. Requires inpatient hospitalization or prolongation of an existing hospitalization. Results in a persistent or significant disability or incapacity. Results in cancer. Results in a congenital anomaly or birth defect.</td>
</tr>
</tbody>
</table>

4.3.3 Adverse event severity grading criteria

4.3.3.1 Phase I studies

The severity of AEs was assessed based on the WHO toxicity criteria and grading scale (Study 100) or an AE scale of mild, moderate or severe, as assessed by the investigator
(Studies 101, 1002, 1004 and 1005). Study 1008 implemented an abbreviated graded severity scale for clinical events based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS), Version 2.0 (2014) and the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

4.3.3.2 Phase II and III studies

The criteria for grading the severity of adverse events in commonly used grading scales were developed for patient populations suffering from diseases such as AIDS (DAIDS) or Cancer (National Cancer Institute Common Toxicity Criteria, NCI CTC) and criteria for grade 4 tend to describe (potentially) life threatening events and those for grade 3 events requiring interventions.

With only grade 1 and 2 for less severe events, and with signs and symptoms of onchocerciasis and Mazzotti reactions for the major part missing, it is impossible to use these scales to obtain the type of differentiated Mazzotti reaction severity profile considered necessary to inform potential use of moxidectin for MDA. Most notable is the lack of sufficient criteria for characterizing ocular safety, a prime consideration for the development of a drug with microfilaricidal properties given the experience with diethylcarbamazine.

Therefore, the Onchocerciasis Chemotherapy Research Center Common Toxicity Criteria (OCRC CTC) criteria were used.

These originate from a scale of 0 to 4 developed by Dr. Awadzi and his collaborators at the OCRC for grading the signs and symptoms of onchocerciasis (Awadzi, K. unpublished) and quantifying the reactions in *O. volvulus* infected individuals to microfilaricidal drugs [9] [10]. The OCRC Mazzotti reaction grading system was combined with elements from the NCI CTC and additional signs and symptoms needed to fully characterize the events observed in participants in OCRC studies.

The OCRC CTC version used in the Phase III study is included in the supplemental appendix to [2]. The version used for the Phase II study did not substantially differ.

The difference between OCRC CTC criteria for grading Mazzotti reactions and the criteria for similar signs and symptoms in the NCI CTC (or other commonly used grading scales), need to be taken into account when interpreting OCRC grades 3 and 4 for Mazzotti reactions.

4.3.4 Laboratory evaluations

**Table 8: Laboratory evaluations by clinical study**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Study 100</th>
<th>Study 101</th>
<th>Study 1002</th>
<th>Study 1004</th>
<th>Study 1005</th>
<th>Study 1008</th>
<th>Phase II</th>
<th>Phase III</th>
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</tbody>
</table>


### 4.3.5 Phase I safety data

Table 9 and Table 10 provide overviews of the adverse events reported in the six Phase I studies. Table 11 shows all adverse events reported in study 1008 by moxidectin dose.
Table 9: All adverse events by moxidectin dose level between 3 mg and 36 mg

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Formulation</th>
<th>Number of Participants /Total Participants (%)</th>
<th>Any AE</th>
<th>ADR</th>
<th>Grade 3 or 4 or severe AE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Withdrawn due to AE</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Liquid or Tablet 6/16 (37.5)</td>
<td>3/16 (18.8)</td>
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<td>0</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>3 mg Fasted</td>
<td>Liquid 4/ 5 (80.0)</td>
<td>4/ 5 (80.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mg Fasted</td>
<td>Tablet 3/10 (30.0)</td>
<td>1/10 (10.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 mg Fasted</td>
<td>Tablet 18/37 (48.6)</td>
<td>8/37 (21.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 mg Fed&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Tablet 31/77 (40.3)</td>
<td>8/77 (10.4)</td>
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<td>0</td>
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<tr>
<td>9 mg Fasted</td>
<td>Liquid 5/ 5 (100)</td>
<td>4/ 5 (80.0)</td>
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<td>9 mg Fed</td>
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<tr>
<td>10 mg Fasted</td>
<td>Liquid 18/29 (62.1)</td>
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<tr>
<td>10 mg Fasted</td>
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</tr>
<tr>
<td>16 mg Fasted</td>
<td>Tablet 1/10 (10.0)</td>
<td>0/10 (0)</td>
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</tr>
<tr>
<td>18 mg Fasted</td>
<td>Liquid 4/ 5 (80.0)</td>
<td>2/ 5 (40.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 mg Fasted</td>
<td>Tablet 1/10 (10.0)</td>
<td>0/10 (0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 mg Fasted</td>
<td>Liquid 4/ 5 (80.0)</td>
<td>4/ 5 (80.0)</td>
<td>1/5 (20.0)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 mg Fasted</td>
<td>Tablet 3/10 (30.0)</td>
<td>0/10 (0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 mg Fed</td>
<td>Liquid 5/ 5 (100)</td>
<td>4/ 5 (80.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>125/259 (48.3)</td>
<td>41/259 (15.8)</td>
<td>1/259 (0.4)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 8 mg dose administered to fed participants in 3110A1-1002-EU (n = 12), 3110A1-1004-EU (n = 38) and 3110A1-1005-EU (n = 27).

<sup>b</sup> In study 3110A1-1004-EU participants received midazolam on Day 1, moxidectin on Day 3 and midazolam again on Day 7 and Day 89. Only AEs after treatment with moxidectin and prior to the second dose of midazolam are included.

<sup>c</sup> WHO toxicity grading scale (Grades 1 – 4) used in 3110A1-100-EU only. Only mild / moderate events reported in other Phase I studies. Events meeting the definition of serious were equivalent across studies.

Table 10: Type of adverse events reported by at least 3% of study participants to the end of follow up across all Phase I studies

<table>
<thead>
<tr>
<th>Dosing</th>
<th>3110A1-100-EU (n = 37)</th>
<th>3110A1-101-EU (n = 58)</th>
<th>3110A1-1002-EU (n = 12)</th>
<th>3110A1-1004-EU (n = 38)</th>
<th>3110A1-1005-EU (n = 54)</th>
<th>MDGH-MOX-1008 (n = 60)</th>
<th>Total with AEs n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common Adverse Events (≥ 3%)</td>
<td>10 mg</td>
<td>8 mg</td>
<td>8 mg</td>
<td>8 mg</td>
<td>4, 8, 16, 24, 36 mg, placebo</td>
<td>Total with AEs n (%)</td>
<td>45 (17.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>13</td>
<td>1</td>
<td>45 (17.4)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>17 (6.6)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12 (4.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>10 (3.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>8 (3.1)</td>
</tr>
</tbody>
</table>
Table 11: Adverse events by moxidectin dose level between 4 mg and 36 mg in Study 1008

<table>
<thead>
<tr>
<th>Preferred Term (MEDRA coding)</th>
<th>MOX (4 mg) n=10</th>
<th>MOX (8 mg) n=10</th>
<th>MOX (16 mg) n=10</th>
<th>MOX (24 mg) n=10</th>
<th>MOX (36 mg) n=10</th>
<th>Placebo n=10</th>
<th>Total N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2.34</td>
</tr>
<tr>
<td>Medical device site reaction</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>Blood cholesterol increased</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>Neck pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2.34</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Hip pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Elevated total bilirubin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>16</td>
</tr>
</tbody>
</table>

4.3.6 Phase II and III study objectives

The primary objective of the Phase II study was to assess the safety of moxidectin. This informed the design as an ‘ascending dose study’ (2 mg, 4 mg, 8 mg moxidectin) with each dose level ‘ascending in intensity of infection’ (mild = skin mf density <10 mf/mg and no ocular involvement, moderate = 10-20 mf/mg and <10 microfilariae across both anterior chamber, severe = >20 mf/mg skin, any level of ocular involvement). Furthermore, the eligibility criteria were designed to select adult women and men who were healthy, except for *O. volvulus* infection (Table 12).

The primary objective of the Phase III study was to compare the effect of a single dose of 8 mg or 150 µg/kg ivermectin on skin microfilariae levels in women and men ≥12 years old. As this study was anticipated to be the last study to include evaluation in a research clinic, extensive safety evaluations were included and the eligibility criteria were designed to be as representative of a ‘potential MDA population’ as was possible based on the safety data from the non-clinical studies, the Phase I studies and the Phase II study and considering the need not to jeopardize efficacy and safety assessments (Table 13).

4.3.7 Phase II and III study eligibility criteria

Table 12: Inclusion and exclusion criteria for Phase II study

<table>
<thead>
<tr>
<th>Phase II Inclusion criteria</th>
<th>Phase II Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and women in good general health, with <em>O. volvulus</em> infection and:</td>
<td>Participation in any studies other than purely observational ones, within 4 weeks before test article administration.</td>
</tr>
<tr>
<td>• Aged 18 to 60 years, inclusive</td>
<td>Any vaccination within 4 weeks before test article administration.</td>
</tr>
<tr>
<td>• Body weight ≥ 40 kg for women and ≥ 45 kg for men</td>
<td>Acute infection requiring therapy within the last 10 days before test article administration.</td>
</tr>
<tr>
<td>• Nonpregnant, non-breast-feeding women. (birth control for women of child-bearing age during the first 150 days after treatment.</td>
<td>Administration of any medication (with the exception of medication required to treat any reactions during the screening fluorescein angiography (chlorpheniramine) or paracetamol) or herbal preparation within 10 days prior to test</td>
</tr>
</tbody>
</table>
### Phase II Inclusion criteria

- Adequate hematologic, renal, and hepatic function, defined as:
  1) White blood cell (WBC) count \( \geq 2,800 \) and \( \leq 11,300 \) cells/mL
  2) Hemoglobin: \( \geq 11.0 \) g/dL for men and \( \geq 10.0 \) g/dL for women
  3) Platelet count: \( \geq 110,000 \) mm\(^3\)
  4) Serum creatinine: \( \leq 1.25 \times \) upper limit of normal (ULN)
  5) Total bilirubin: \( \leq 1.25 \times \) ULN
  6) AST/SGOT: \( \leq 1.25 \times \) ULN
  7) AP: \( \leq 1.25 \times \) ULN
  8) Prothrombin time WNL
  9) Urinalysis WNL

### Phase II Exclusion criteria

- article administration or any condition currently requiring regular medication
- Clinically significant ECG abnormalities or history of cardiac abnormality
- Past or current history of neurological or neuropsychiatric disease or epilepsy
- Orthostatic hypotension at the screening evaluation
- History of drug or alcohol abuse or regular use of \( \geq 3 \) cigarettes per day
- Use of alcohol or other drugs of abuse within 72 hours before test article administration
- Any condition, in the investigator’s opinion, that places the subject at undue risk
- Subjects who have donated blood within 8 weeks before study entry
- Subjects with ocular onchocerciasis in cohorts intended to enroll subjects with mild infection. Ocular onchocerciasis is defined by the presence of live or dead microfilariae, onchocercal punctate opacities, onchocercal lesions of the posterior segment or lesions that mimic those seen in onchocerciasis.
- Subjects with hyperreactive onchodermatitis
- Antifilarial therapy within the previous 5 years
- Coincidental infection with Loa Loa

### Table 13: Inclusion and exclusion criteria for Phase III study

<table>
<thead>
<tr>
<th>Phase III Inclusion criteria</th>
<th>Phase III Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male or female</td>
<td>Chosen in consideration of safety data available from pre-clinical and clinical studies or based on experience with ivermectin</td>
</tr>
<tr>
<td>At least 12 years of age</td>
<td>Pregnant or breastfeeding women</td>
</tr>
<tr>
<td>Weighing at least 30 kg</td>
<td>Loiasis co-infection*</td>
</tr>
<tr>
<td>Onchocerca volvulus infection, at least 10 microfilariae/mg (mean of 4 skin snips)</td>
<td>Known or suspected allergy to moxidectin or ivermectin</td>
</tr>
<tr>
<td>Reliable method of birth control for woman of childbearing potential</td>
<td>Any concomitant condition that would preclude an evaluation of a response or would place subject’s health at undue risk.</td>
</tr>
</tbody>
</table>

Chosen in view of ensuring safety and efficacy assessments would not be jeopardize

- Prior treatment with diethylcarbamazine, suramin, ivermectin, albendazole or levamisole within 6 months before planned test article administration
- Lymphatic filariasis with an intensity of infection \( >100 \) mf/mL* 
- Acute or uncontrolled disease process within 7 days before test article administration. Patients with stable chronic diseases (e.g., no change in medication for past month) were permitted.
- Received any investigational drugs or devices within 4 weeks

* Study areas were neither loiasis nor lymphatic filariasis endemic.
4.3.8 Characterization of adverse events in Phase II and III studies by each investigator and central expert review

Each investigator had to provide the following characteristics for each adverse event:

- Start and stop date
- Severity
- Mazzotti reaction: Yes or no
- For AEs not considered Mazzotti reaction: reasonable causal relationship to study drug
  - Phase II study: definitely, probably, possibly, probably not, definitely not.
  - Phase III study: Yes or no
- Outcome:
  - Phase II study: Resolved, Sequelae upon resolution, Persisted, Death
  - Phase III study: Resolved, Persisted, Death
- Action taken:
  - None, withdrawn from study, hospitalized or prolonged hospitalization, medication prescribed, other action (specify)
- Serious Adverse Event: Yes or No

Furthermore, prior to unblinding, all adverse events data reported by all investigators in the data base were reviewed centrally by one expert reviewer for assessment of whether an AE was a Mazzotti reaction or not and if not whether it an ADR or not. The outcome of this central review was added to the data base. The data provided in Opoku et al. [2] are based on the outcome of the central review, while the data submitted to the US FDA are based on individual investigator assessment.
4.3.9 Phase II and III study safety evaluations

Table 14: Safety evaluations in Phase II study

| Safety evaluations                          | D-4 to D-2 | D-1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 | D15 | D16 | D17 | D18 | M1 | M2 | M3 | M6 | M12 | M18 |
|-------------------------------------------|------------|-----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|-----|-----|
| Medical history                           | X          |     |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |    |    |    |    |     |     |
| Medication history                        | X          |     |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |    |    |    |    |     |     |
| Physical Exam                             | X          |     |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |    |    |    |    |     |     |
| Height                                    | X          |     |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |    |    |    |    |     |     |
| Weight                                    | X          | X   | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | M3 | M6 | M18 |     |
| Vital signs                                | X          | X   | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | M1 | M2 | M3 | M6 |
| 12 lead ECG                               | X          | X   | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | M2 | M3 | M6 | M12 |
| Ocular exama                              | X          | X   | X  | X  |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Retinal Colour Photographs and Fluorescein angiogramb | X          |     |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Interim physical examination              | X          | X   | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |     |     |     |     |
| Hematologyc                               | X          | X   | X  | X  |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Serum chemistyd                          | X          | X   | X  | X  |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Urinalysisa                              | X          | X   | X  | X  |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Adverse events                            | X          | X   | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |     |     |     |     |

- a: visual acuity, visual fields using a calibrated Goldmann perimeter, color vision, external ocular structures, ocular mobility and pupillary reflex, intra-ocular pressure, dilated fundus examination with direct and indirect ophthalmoscopy, anterior segment examination with slit-lamp,
- b: For all participants until month 3, then only in those with lesions or visual defects,
- c: prothrombin time, complete blood cell count (CBC), including hematocrit, hemoglobin, WBC with differential, platelet count, examination for microfilariae,
- d: sodium, potassium, chloride, bicarbonate, glucose, total protein, albumin, urea, creatinine, alkaline phosphatase, lactic dehydrogenase (LDH), total bilirubin, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT),
- e: Specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, microscopic evaluation, examination for microfilariae.

D Day, M Month.

Each participant received four identical looking capsules with the study drug they had been randomized to on the morning of D1.
Table 15: Safety evaluations in Phase III study

<table>
<thead>
<tr>
<th>Safety evaluations</th>
<th>D-30 to -1</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D6</th>
<th>D14</th>
<th>M1</th>
<th>M3</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Medication history</td>
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<td></td>
<td></td>
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<tr>
<td>Height</td>
<td>X</td>
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</tr>
<tr>
<td>Weight</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Physical examination</td>
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<td>Vital signs</td>
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<tr>
<td>12-Lead ECG</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ocular examination&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum chemistry&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Urinalysis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Adverse events</td>
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<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>: visual acuity, anterior segment examination with up to x25 slit lamp, dilated fundus examination by direct and indirect ophthalmoscopy, color vision examination, intraocular pressure, visual field examination, ocular mobility, pupillary reflex examination, and external ocular structures examination.

<sup>b</sup>: Total white blood cell count with differential, platelet count, hemoglobin, and hematocrit.

<sup>c</sup>: serum chemistry tests including sodium, potassium, chloride, glucose, blood urea nitrogen (BUN) or urea, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase (AP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), aspartate aminotransferase (SGOT) (AST), and alanine aminotransferase (SGPT) (ALT).

<sup>d</sup>: specific gravity, pH, albumin (protein), glucose, ketones, hemoglobin, bilirubin, urobilinogen, nitrite, leukocyte esterase. Microscopic evaluation of red blood cells, WBC, epithelial cells, bacteria, casts, and crystals at baseline and thereafter only at investigator’s discretion as medically indicated.

D Day, M Month.

Each participant received four identical looking capsules with the study drug they had been randomized to on the morning of D1.
### 4.3.10 Phase II efficacy data

Figure 8 and Figure 9 show that the skin microfilariae levels after a single 8 mg dose of moxidectin or the standard dose of ivermectin in the Phase II study display changes over time consistent with those in the Phase III study.

**Figure 8**: Skin microfilariae densities 8 days, 1, 2, 3, 6, 12 and 18 months after a single 8 mg dose of moxidectin or the standard dose of ivermectin relative to pre-treatment density for each participant in the Phase II study.
4.3.11 Additional Phase III efficacy and safety data

There was no statistically significant difference in the reduction in ocular microfilariae between moxidectin and ivermectin treated participants [2].

Figure 10 demonstrates that neither the microfilaricidal efficacy of moxidectin, nor that of ivermectin differ substantially by dose per kg.
Figure 10: Mean skin mf density 1 month after treatment with moxidectin or ivermectin by weight-based drug exposure

Figure 11 shows the severity of Mazzotti reactions, grouped by Mazzotti reaction cluster, across all pre-treatment skin mf densities and by range of pre-treatment densities . [2].

Figure 11: OCRC CTC Severity of different clusters of Mazzotti reactions across all and by range of pre-treatment skin mf density after treatment with 8 mg moxidectin or 150 µg/kg ivermectin (adapted from [2] supplementary appendix)

ClinMaz – clinical Mazzotti reaction, OculMaz – ocular Mazzotti reaction, HemMaz – hematological Mazzotti reaction, BiochemMaz – biochemical Mazzotti reaction. G - Grade
Figure 12: OCRC CTC Severity of different clinical Mazzotti reactions across all and by range of pre-treatment skin mf density after treatment with 8 mg moxidectin or 150 µg/kg ivermectin (adapted from [2] supplementary appendix)
Figure 13: OCRC CTC Severity of for different laboratory Mazzotti reactions across all and by range of pre-treatment skin mf density after treatment with 8 mg moxidectin or 150 µg/kg ivermectin (adapted from [2] supplementary appendix)
Figure 14: OCRC CTC Severity of for different ocular Mazzotti reactions across all and by range of pre-treatment skin mf density after treatment with 8 mg moxidectin or 150 µg/kg ivermectin (adapted from [2] supplementary appendix)
Figure 15: Percentage of participants by post-treatment time period for resolution of their Mazzotti reactions.

Figure 16: Cumulative percentage of participants with clinical Mazzotti reactions (A, B) and ocular Mazzotti reactions (C, D) by day after treatment the reaction started (A,C) and resolved (B,D).
4.4 Overview of information included in the New Drug Application to the US FDA

Figure 17 shows selected statistics on the data and reports included in the NDA and US FDA review. The US FDA approved labelling (package insert) and the FDA review summaries are available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApp

![Diagram of data elements included in the NDA and FDA review](image)

Figure 17: Selected statistics on elements included in the NDA to the US FDA and US FDA review times and outputs

CMC: Chemistry, Manufacturing and Control, cGMP current Good Manufacturing Practice

4.5 Graphic presentation of design of ongoing studies of moxidectin for onchocerciasis

![Diagram of Pediatric dose finding study design](image)

Figure 18: Design of Pediatric dose finding study (MDGH-MOX-1006)
Figure 19: Design of repeat dose efficacy and safety study (MDGH-MOX-3001)
mf skin microfilariae, R, randomization, Rx active treatment, PL placebo,
Note: sample size per arm may change under protocol amendment to reach a total of n=320 -350..

Figure 20: Design of single dose safety study (MDGH-MOX-3002)

5 References

Reference List


