Presentation outline

- Background
- Rationale for the technical consultation
- Objectives
- Main meeting conclusions
- Key knowledge gaps
- Proposed Target Product Profile
Background
Ivermectin is an antiparasitic medicine approved for the control and treatment of:

- Onchocerciasis
- Strongyloides
- Lymphatic filariasis
- Scabies

It blocks neurotransmission in invertebrates by binding to the glutamate-gated chlorine channels.

It is an endectocide, a systemic insecticide that can kill arthropods (such as anopheles mosquitoes) that feed on treated individuals (pre-read annex 1).
How could it be used in malaria control?

- Mass drug administration with ivermectin has the potential to be a complementary tool to reduce malaria transmission, particularly in:
  - Settings where vectors bite in temporal and spatial gaps left by ITNs and IRS (exhophili, exophagi, early biting, early exit)
  - Areas with insecticide resistance. Ivermectin has a different mechanism of action from all public health insecticides
  - Settings where transmission persists despite implementation of all effective vector control interventions
Rationale for the technical consultation
Rationale for the technical consultation

- There is a renewed interest among researchers and other stakeholders.

- Yet research has been uncoordinated. The multiplicity of research questions and endpoints have failed to produce evidence capable of having an impact on policy formulation.

- The GMP and NTD department jointly organized the technical consultation with the following objectives:
Objectives

General objective

- To define the key missing data to make a policy recommendation on the use of ivermectin in malaria transmission reduction. This would be aided by the development of a target product profile (TPP) for ivermectin as a tool to reduce malaria transmission.
Objectives

Specific objectives

- Define the experimental data needed to establish the regimen of ivermectin (minimum efficacy for transmission) that could be used to reduce transmission & how to measure.
- Define relevant delivery strategies for deployment to achieve the desired impact.
- To identify any additional gaps in knowledge which would be needed to support the implementation of ivermectin in resource poor settings.
- Evaluate the clinical development and regulatory pathways for ivermectin as a tool for reducing malaria transmission.
Main meeting conclusions
Main meeting conclusions

- Ivermectin MDA could reduce vectorial capacity primarily by reducing vector survival and fitness, but also, to a lesser extent, through a potential partial inhibition of sporogony and additional effects on vector fertility.

- This potential new application of ivermectin deserves full understanding, particularly its role in: (a) reducing the residual transmission of malaria, (b) curbing insecticide resistance and (c) accelerating progress towards elimination.

- Research should be guided by Target Product Profile designed on the expected public health role of ivermectin for malaria control. The critical components of the TPP will be efficacy, safety and regulatory/policy requirements.
Efficacy

• The efficacy of ivermectin MDA to reduce malaria transmission will be directly related to the blood drug levels, the duration of these blood levels and the population coverage.
• The duration of the blood levels is the factor that drives impact.
• The FDA approved ivermectin regimen for onchocerciasis of a single yearly dose of 150 mcg/kg is unlikely to achieve the desired impact on malaria transmission.
• The impact could be increased by pharmacological strategies such as using higher single doses, repeated dosing, or new formulations allowing longer term plasma exposure.
• Ivermectin will be deployed with other forms of vector control and could be deployed in combination with a parasite focused MDA. This could facilitate efficiency of delivery but faces a more complex regulatory pathway.
Main meeting conclusions

Safety

• Ivermectin has a wide safety margin for its current use. This margin is lower for malaria transmission reduction since this would require a higher dose and/or sustained plasma exposure.

• Pre-clinical studies in pregnant mice, rats and rabbits show teratogenicity at doses that were toxic to the mother. There is no systematic database of inadvertent exposure in pregnancy.

• Ivermectin has been deployed at 150 mcg/kg in millions of individual in onchocerciasis/LF control programs. Data from very small trials with healthy volunteers suggest that higher single doses (up to 2,000 mcg/kg) are also safe.

• The *Loa loa*-associated encephalopathy is the most serious clinical adverse event.

• There is no evidence that deployment of ivermectin for malaria transmission control would produce any additional safety issues due to interactions with nematodes.
Main meeting conclusions

Regulatory and policy pathways

- The primary policy question is to **clearly define what safety and efficacy data are required to support a WHO policy recommendation for ivermectin as a tool to reduce malaria transmission**. Consultation with the relevant regulatory agencies and policy makers from countries to determine what additional data they would need to deploy the regimen would be an important next step.

- Prior to deployment, it would be important to have approval of the use by a stringent regulatory authority or WHO-Prequalification. Approval of the product in the country of manufacture will also be critical.

- Repurposing pathways such as FDA´s 505(b)(2) or equivalent in other agencies could be appropriate, an in-depth review of the clinical safety data would be required.
Main meeting conclusions

Market and supply

- Currently ivermectin is donated by one supplier. Prequalification of multiple suppliers may be critical to maintaining stability of supply, and also for achieving an appropriate price for procurement through United Nations agencies or the Global Fund.

- It should not be assumed that the current donation program will or even can be extended to cover malaria transmission reduction.
Key knowledge gaps
Key knowledge gaps

Efficacy

- The exposure response for insect lethality determined via direct skin-feeding on humans. **Understanding of the LC$_{50}$ for all key insect vector species.**
- Studies need to be conducted on children and those with co-infections in order to understand the factors which might impact on plasma exposure.
- Evaluate the potential for *Anopheles* mosquitoes to develop resistance to ivermectin, and if proven, develop laboratory based resistance markers before wide scale deployment.
- Validation of lab-based entomological endpoints to assess ivermectin’s efficacy and their correlation with epidemiological impact would be desirable.
Key knowledge gaps

Safety

• **Acceptable safety profile of ivermectin used at higher doses, or longer regimens**, which would be required to achieve LC$_{50}$ levels for the main vectors for a significant period of time.

• Analysis of whether the current safety windows in preclinical safety studies, for normal animals, juveniles and in EFT studies support more frequent or increased dosing.

• Analysis of the current safety data based in children less than 15 kg.

• Establishment of pregnancy registries to investigate safety in inadvertent exposure in pregnancy especially in the early first trimester.

• **In the long term, new diagnostics and strategies to prevent Loa-related adverse effects.**
Key knowledge gaps

Regulatory and policy pathways

- *To clearly document through consultation* the evidence that would best inform a policy recommendation on the use of ivermectin to reduce malaria transmission.

- Operational data on cost effectiveness and delivery mechanisms, and discussions with the disease endemic countries as to the thresholds required for introduction into health policy.

- Consultation with WHO Prequalification as to the data requirements for use of an already prequalified medicine for use in a new indication

- Identification of other ICH approved manufacturers to produce alternative supplies of ivermectin to reduce the risk of dependence on a single supplier.
Proposed Target Product Profile
<table>
<thead>
<tr>
<th>Efficacy threshold</th>
<th>Desired</th>
<th>Minimally acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination with an ACT and core vector control interventions</td>
<td>A significant reduction in incidence of clinical malaria at 12 months after a single intervention in combination with ACT MDA and core vector control measures.</td>
<td>A significant reduction in infection incidence at 12 months after three interventions given at monthly intervals in combination with an ACT MDA and core vector control measures.</td>
</tr>
</tbody>
</table>
| Free standing insecticide | **At least 20% reduction of incidence of clinical malaria lasting for at least one month after a single round of MDA irrespectively of baseline transmission levels.** | **In areas of moderate to high transmission:**  
At least 20% reduction of infection incidence in children under 5, lasting for at least one month, following a single regime.  
**In areas of low transmission:**  
A significant reduction of infection incidence, lasting for at least one month following a single regime. |
<table>
<thead>
<tr>
<th>Target population</th>
<th>Desired</th>
<th>Minimally acceptable</th>
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</thead>
<tbody>
<tr>
<td>Target</td>
<td>Rationale</td>
<td>Target</td>
</tr>
<tr>
<td>Acceptable in children 5-15 kg (children &lt; 90 cm as proxy)</td>
<td>Increasing coverage is expected to be directly related to a higher efficacy. This will however depend on the exposure of children and pregnant women to malaria transmission.</td>
<td>All population in the target areas with the exception of: - Pregnant women - Lactating women in the first week after birth - Children &lt; 15 kg (&lt; 90 cm as proxy) - The severely ill</td>
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<tr>
<td>Acceptable in women in reproductive age without a pregnancy test</td>
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<tr>
<td>Acceptable in pregnant women</td>
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<tr>
<td>Acceptable in lactating women</td>
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</tbody>
</table>

At population level efficacy will be directly related to coverage.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Desired</th>
<th>Rationale</th>
<th>Minimally acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage &amp; schedule</td>
<td><strong>Single-dose administration of a slow-release formulation.</strong></td>
<td>Administration in a single encounter will facilitate compliance and allow for directly observed therapy. High adherence will be directly related to effectiveness and, together with therapeutic efficacy contribute to the effective coverage.</td>
<td>Single-encounter, manageable multiple dose scheme (once a day for up to three days with or without an ACT)</td>
</tr>
<tr>
<td></td>
<td>The cumulative dose (mcg/kg/day) best matched with the AUC needed for the efficacy target.</td>
<td></td>
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<tr>
<td></td>
<td>Cmax below the theoretic mosquito LC(_{100}) desirable.</td>
<td></td>
<td>The main advantage is the use of the current dosage and existing formulation.</td>
</tr>
<tr>
<td></td>
<td>Should be timed to malaria transmission season</td>
<td></td>
<td>Up to 1400 mcg/kg within a month is the dose recommended by the CDC for crusted scabies</td>
</tr>
<tr>
<td>Parameter</td>
<td>Desired</td>
<td>Minimally acceptable</td>
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</tr>
<tr>
<td></td>
<td>Target</td>
<td>Rationale</td>
<td>Target</td>
</tr>
<tr>
<td>Formulation</td>
<td>Slow release (non-injectable)</td>
<td>This approach could allow for administration on a single encounter and maximization of the AUC : efficacy ratio</td>
<td>Current oral formulation (3 or 6 mg tablets) used in multiple doses.</td>
</tr>
<tr>
<td>Parameter</td>
<td>Desired</td>
<td>Minimally acceptable</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Target</td>
<td>Rationale</td>
<td>Target</td>
</tr>
<tr>
<td>Safety profile</td>
<td>Incidence of adverse events of total dose/body-weight/timeframe less than 1: 10,000</td>
<td>This is the current threshold proposed by MMV for the development of novel malaria drugs.</td>
<td>No severe adverse drug reactions AND frequency of moderate adverse events ≤ 1.3 %.</td>
</tr>
<tr>
<td></td>
<td>New strategy available for risk minimisation in Loa endemic areas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Desired Target</td>
<td>Desired Rationale</td>
<td>Minimally acceptable Target</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Drug-to-drug interactions</td>
<td>No significant interaction with antimalarials, ARV, TB drugs and antihelminthics.</td>
<td>Co-endemicity of NTDs and malaria. Longer-lasting formulations would have a larger cumulative dose and likelihood of co-administration.</td>
<td>No significant interactions with ACTs, primaquine, transmission-blocking vaccine candidates</td>
</tr>
<tr>
<td>Parameter</td>
<td>Desired</td>
<td>Minimally acceptable</td>
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</tr>
<tr>
<td></td>
<td>Target</td>
<td>Rationale</td>
<td>Target</td>
</tr>
<tr>
<td>Manufacturability</td>
<td>Production process fully scalable to meet also the requirements for NTDs and malaria. Commitment of multiple potential suppliers with prequalified products or approved by stringent regulatory authorities.</td>
<td>There is no current pharmaceutical alternative to ivermectin for the control of onchocerciasis. <strong>Procurement of ivermectin for malaria should not affect the global production and supply for the control and elimination of NTDs.</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Feasibility & related concepts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Desired</th>
<th>Minimally acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Packaging &amp; presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target</td>
<td></td>
<td>Adequate programmatic suitability for MDA campaigns.</td>
</tr>
<tr>
<td>Rationale</td>
<td></td>
<td>Cost-reduction strategies need to be considered early in the development of new dosage regimens and formulations.</td>
</tr>
<tr>
<td><strong>Shelf life &amp; storage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable for at least 60 months at 37 °C and 75% humidity.</td>
<td>Target based on MMV´s TPPs.</td>
<td>Stable for at least 24 months at 37 °C and 75% humidity.</td>
</tr>
</tbody>
</table>
## Cost

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Desired</th>
<th>Minimally acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target</td>
<td>Rationale</td>
</tr>
<tr>
<td><strong>Cost of goods</strong></td>
<td>&lt; 0.2 US$</td>
<td>Based on costs of the API</td>
</tr>
<tr>
<td><strong>Cost-effectiveness</strong></td>
<td>US$ 2.20 (0.88-9.54) for one year of protection per person</td>
<td>The estimated cost/person/year of protection of LLINs. Cost per case averted is likely to be a better parameter for ivermectin.</td>
</tr>
<tr>
<td>Parameter</td>
<td>Desired</td>
<td>Minimally acceptable</td>
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<td>-----------</td>
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</tr>
<tr>
<td></td>
<td><strong>Target</strong></td>
<td><strong>Rationale</strong></td>
</tr>
<tr>
<td>Registration and WHO prequalification</td>
<td>Use approved or product licensed by a stringent regulatory agency. More than one supplier with approval by stringent regulatory authority or prequalified by WHO</td>
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</tbody>
</table>
The *Loa loa* challenge

- Individuals with high *Loa loa* microfilaremia (>30,000 mf/ml) are at risk of SAEs including fatal encephalopathy with ivermectin treatment
- Current strategies by the NTD program include avoidance of highly endemic areas and assurance of means to handle adverse reactions in the localities where risk benefit warrants treatment (do not treat with steroids, IV lines, bag and mask devices...)
- Geographic overlap *Loa loa* – malaria creates risk for new malaria indication
Emerging strategy to solve *Loa loa*

1. **Exclusion**

Modelling of high risk communities based on prevalence data. Presumed rate of high risk has dropped from about 5% to 3%
Emerging strategy to solve *Loa loa*

2. Test and (not) treat strategy

"Point-of-care", quick and reliable **quantification** of *Loa loa* in blood allows exclusion of high risk individuals

(a) **Cellscope**: accurate quantitative results in 2 minutes. Tested successfully in 15,000 population and now moving into second stage.

- Early result suggest prevalence of high risk is lower than expected (<3%)

(b) New biomarkers

**Identification and Validation of Loa loa Microfilaria-Specific Biomarkers: a Rational Design Approach Using Proteomics and Novel Immunoassays**

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Helminth Immunology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA; Protein Characterization Laboratory, Frederick National Laboratory for Cancer Research, Leidos, Inc., Frederick, Maryland, USA.*

* Present address: Jesica A. Herrick, Division of Infectious Diseases, Immunology, and International Medicine, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA; Timothy D. Veenstra, Department of Applied Science, Maranatha Baptist University, Watertown, Wisconsin, USA.
Emerging strategy to solve *Loa loa*

3. LF elimination

Impressive results on LF post single administration of triple therapy offers rapid pathway to LF elimination. This treatment also reduces *Loa loa burden* and thus risks from ivermectin for any indication (including malaria).

*To be worked out: are the risks different from higher doses, or from different regimens?*
Solving *Loa loa* is a priority for NTD community. Emerging tools and strategies being advanced currently, creating a near term window of opportunity for malaria.

- New diagnostic tools (*Loascope*) make population level screening possible.
- Promising LF elimination with the new test and (not) treat strategy may offer a programmatic Approach to addressing the Loa barrier to ivermectin treatment. Additionally, if the test and treat strategy for Loa/oncho roles out this will decrease the Loa burden and pre-screen populations at risk that will help with further ivermectin use.
- Triple drug regimen will also be tested in Loa areas with LF and potentially oncho which could further decrease the Loa issue.