Global **Malaria** Programme

WHO preferred product characteristics: endectocide for malaria transmission control

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INFORMATION NOTE

BACKGROUND

One of the key supporting elements of the *Global Technical Strategy for Malaria 2016–2030* is to harness innovation and expand research *(1)*. To accelerate progress towards elimination and to counteract the emerging threats posed by drug and insecticide resistance, efforts should be centred on fostering innovation and developing new tools and actions to facilitate the introduction of new products and strategies.

Endectocides are antiparasitic drugs active both against endoparasites and against ectoparasites. Ivermectin is a member of the macrocyclic lactone class of endectocides, commonly referred to as avermectins. Ivermectin is a broad-spectrum antihelminthic medicine that is used extensively for the control of onchocerciasis and lymphatic filariasis (LF) was used as a prototype in the development of this Preferred Product Characteristics (PPC).

In vitro studies have shown that ivermectin causes the death of *Anopheles* mosquitoes that ingest sufficient doses in a blood meal *(2-6)*. These results have been confirmed in clinical studies using membrane *(7)* and direct-feeding *(8)* methodologies. Modelling based on these studies indicates that MDA with ivermectin has the potential to reduce malaria transmission *(9, 10)*, mainly by negatively impacting mosquito survival, fitness, and fertility, and potentially inhibiting sporogony.

Although there has been a marked increase in the research on this topic in recent years, the different methods used and heterogeneity of study outcomes have limited comparability and precluded a systematic analysis of the evidence.

World Health Organization

WHO/HTM/GMP/2017.10

The WHO Global Malaria Programme and the Department for Control of Neglected Tropical Diseases jointly convened a technical consultation meeting with an objective to develop a preferred product characteristics that would define the key questions that an endectocide (using ivermectin as a prototype) research agenda should address to generate the appropriate evidence required to define a WHO policy position on the role of an endectocide in the reduction of malaria transmission. The PPC presented in this document has been endorsed by the WHO Malaria Policy Advisory Committee.

POSSIBLE PREFERRED PRODUCT CHARACTERISTICS COMPONENT FOR AN ENDECTOCIDE AS A VECTOR CONTROL TOOL

Mosquitocidal efficacy of ivermectin and its pharmacokinetic properties

Two key factors influence the efficacy of ivermectin for reducing malaria transmission.

1. the plasma levels reached after a given dose: mosquito mortality is related to ivermectin blood concentration in a dose-dependent manner, and

2. the duration the plasma concentration is sustained above the lethal concentration 50 (LC50).

Conclusions

- Mosquito mortality is directly related to (a) the concentration of ivermectin and its metabolites in the blood (i.e., dose-response gradient) being above a known threshold that is lethal to the mosquito and (b) the duration of such concentration levels and percentage of blood sources treated with the medicine;

- The endectocidal effect is driven by the length of time above the LC_{50}, rather than the maximum concentration of ivermectin;

Potential entomological endpoints for assessing the efficacy of ivermectin

The LC_{50} is an entomological parameter that is used to assess the susceptibility of any given mosquito species to the lethal effect of a chemical agent.

Conclusions

- Any proposed entomological outcome measures of ivermectin efficacy should be validated against a proven human epidemiological impact;

- A reduction of at least 20% in clinical malaria incidence lasting for at least 1 month after a single round of ivermectin MDA was considered to be a target of public health relevance over the long term.

Potential surrogate markers of the effect of ivermectin on malaria transmission

Ivermectin affects nearly all aspects of vectorial capacity (i.e., survivorship, re-feeding frequency, vector competence for Plasmodium)

Conclusions

1. Entomological
    - Mosquito mortality (measured by the LC50 as indicated above)
    - Reduced mosquito fitness and fertility
    - Mosquito population age structure as measured by parity rates
    - Mosquito density
    - Mosquito biting rate, measured directly or by human antibody response
2. Entomological-parasitological
    - Sporozoite index, as markers of sporogony inhibition by ivermectin in the blood meal
    - Variations in the entomological inoculation rate (EIR), resulting from direct and indirect mosquito killing and the effect of ivermectin on the completion of the sporogonic cycle

PROPOSED PREFERRED PRODUCT CHARACTERISTICS

EFFICACY		
	DESIRED	**MINIMALLY ACCEPTABLE**
Stand-alone insecticide	In all transmission settings, at least 20% reduction[1] in the incidence of clinical malaria, lasting for at least 1 month after a single round of MDA irrespective of baseline transmission levels	**In areas of moderate to high transmission:** At least 20% reduction in the incidence of clinical malaria (as primary outcome) and incidence of infection (as secondary outcome) in children under 5, lasting for at least 1 month following a single regimen **In areas of low transmission:** A reduction in infection incidence, lasting for at least 1 month following a single regimen
Effect on vector as an interim endpoint	In high to moderate transmission settings, at least 80%[2] reduction in the entomological inoculation rate (EIR[3]) in intervention arm compared to control arm when dealing with a largely anthropophilic vector species, and EIR reduction of <80% when dealing with zoophilic vectors	In high to low transmission areas, a significant reduction of the parity rate and vector density (no threshold) in intervention arm compared to control arm

EFFICACY-RELATED CONCEPTS				
	DESIRED		**MINIMALLY ACCEPTABLE**	
Parameter	**Target**	**Rationale**	**Target**	**Rationale**
Target population	Acceptable in all age groups including children 5–15 kg Acceptable in women of reproductive age without a pregnancy test Acceptable in pregnant women Acceptable in lactating women	An increase in coverage is expected to be directly related to greater efficacy. This will, however, depend on the exposure of children and pregnant women to malaria transmission.	All populations in the target areas, with the exception of: • Pregnant women • Lactating women in the first week postpartum • Children < 15 kg • The severely ill	Coverage with this limitation in the RIMDAMAL study *(11)* was 72%. At population level, efficacy will be directly related to coverage.
Dosage & schedule	Single-dose administration of a slow-release formulation The cumulative dose (mcg/kg/day) best matched to the area under the curve (AUC) needed for the efficacy target C_{max} below the theoretical mosquito LC_{100} Timed to malaria transmission season	Administration in a single encounter will facilitate compliance and enable directly observed therapy. High adherence will be directly related to effectiveness and, together with therapeutic efficacy, contribute to effective coverage. A challenge with this approach is the significant R&D investments that would be needed to develop a new formulation.	Single-encounter, manageable multiple-dose scheme (e.g. once a day for up to 3 days)	The use of the current dosage and existing formulation. Challenges include: adherence, the safety of higher Cmax, and a theoretical limit to efficacy once the mosquito LC100 is reached.

Formulation	Slow-release (non-injectable) for single dose administration	This approach could allow for administration in a single encounter and the maximization of the AUC:efficacy ratio.	Oral formulation used in multiple doses	
SAFETY & RELATED CONCEPTS				
	DESIRED		**MINIMALLY ACCEPTABLE**	
Parameter	**Target**	**Rationale**	**Target**	**Rationale**
Safety profile	Incidence of adverse events of total dose/body weight/timeframe less than 1:10 000 Strategy available for risk minimization in specific high risk situations e.g. ivermectin in Loa loa-endemic areas	This is the current threshold proposed by MMV for the development of novel malaria drugs *(12)*.	No severe adverse drug reactions AND frequency of moderate adverse events ≤ 1.3 % Defined strategy for risk minimization in specific high risk situation e.g. *Loa loa*-endemic areas or exclusion in those situations.	This is the frequency of the moderate adverse events observed in onchocerciasis control campaigns *(13)*.
Drug–drug interactions	No significant interaction with antimalarials, ARV, TB drugs and antihelminthics If longer-lasting formulations or schemes are proposed, the safety of co-administration with common over-the-counter drugs should also be evaluated.	Co-endemicity of NTDs and malaria; longer-lasting formulations would have a larger cumulative dose and greater likelihood of co-administration.	No significant interactions with ACTs, primaquine, or transmission-blocking vaccine candidates	These interventions are likely to be used together in elimination settings.
FEASIBILITY & RELATED CONCEPTS				
	DESIRED		**MINIMALLY ACCEPTABLE**	
	Target	**Rationale**	**Target**	**Rationale**
Manufactur-ability			Production process fully scalable to meet the requirements for NTDs and malaria Commitment of multiple potential suppliers with prequalified products or approval from stringent regulatory authorities	There is no current pharmaceutical alternative to ivermectin for the control of onchocerciasis. Procurement of ivermectin for malaria should not affect the global production and supply for the control and elimination of NTDs.
Packaging & presentation			Adequate programmatic suitability for MDA campaigns	Cost-reduction strategies need to be considered early in the development of new dosage regimens and formulations.

Shelf life & storage	Stable for at least 60 months at 37 ºC and 75% humidity	Target based on MMV´s TPPs *(12)*	Stable for at least 24 months at 37 ºC and 75% humidity	The current label recommends storage below 3 ºC. This is the minimum acceptable target based on MMV´s TPPs (12).
COSTS				
	DESIRED		**MINIMALLY ACCEPTABLE**	
	Target	**Rationale**	**Target**	**Rationale**
Cost–effectiveness	US$ 2.20 (0.88–9.54) for 1 year of protection/person	The estimated cost/person/year of protection of LLINs (14)	US$ 6.70 (2.22–12.85) for 1 year of protection/person	The estimated cost/person/year of protection of IRS (14)
REGISTRATION				
	DESIRED		**MINIMALLY ACCEPTABLE**	
	Target	**Rationale**	**Target**	**Rationale**
Registration and WHO-PQ	Use products approved or licensed by a stringent regulatory agency. More than one supplier with approval from a stringent regulatory authority or prequalified by WHO		One supplier with product approved by stringent regulatory agency or prequalified by WHO Country registration	Approval by a stringent regulatory agency or WHO-PQ is the requirement for procurement by the Global Fund and many agencies.

Notes

1 The desired effect size is an increase over baseline effect of standard prevention intervention e.g. LLIN compared to a control arm with only the standard preventive intervention.

2 Based on two studies in West Africa showing a reduction on sporozoite rate by 79% (Kobylinski et al (AJTMH 2011; 85: 3-4) and 77% (Alout et al Malaria J 2014; 13: 417) in areas with *An gambiae* s.l. where IVM MDA was administered for two weeks post MDA in treatment villages in intense transmission seasons. Robust study designs should be observed as proposed by Wilson et al. Trends Parasitol. 2015 Aug;31(8):380-90.

3 Assuming standardised methods for measuring EIR parameters based on systematic sampling across demographic and ecological settings. Vector species composition (including sibling species) and human biting index by species is essential to know before the start and during the trial.

REFERENCES

1. WHO: Global technical strategy for malaria 2016-2030. http://wwwwhoint/malaria/publications/atoz/9789241564991/en/ (accessed June 2016).

2. Iakubovich V, Zakharova NF, Alekseev AN, Alekseev EA: [Evaluation of the action of ivermectin on blood-sucking mosquitoes]. Med Parazitol (Mosk) 1989:60-64.

3. Jones JW, Meisch MV, Meek CL, Bivin WS: Lethal effects of ivermectin on Anopheles quadrimaculatus. J Am Mosq Control Assoc 1992, 8:278-280.

4. Fritz ML, Siegert PY, Walker ED, Bayoh MN, Vulule JR, Miller JR: Toxicity of bloodmeals from ivermectin-treated cattle to *Anopheles gambiae* s.l. Ann Trop Med Parasitol 2009, 103:539-547.

5. Kobylinski KC, Deus KM, Butters MP, Hongyu T, Gray M, da Silva IM, Sylla M, Foy BD: The effect of oral anthelmintics on the survivorship and re-feeding frequency of anthropophilic mosquito disease vectors. Acta Trop 2010, 116:119-126.

6. Kobylinski KCP, Alongkot; Ubalee, Ratawan; Schuster, Anthony; McCardle, Wes; Foy, Brian D; Tarning, Joel; Szumlas, Dan E; Richardson, Jason H. : Assessing ivermectin susceptibility of Greater Mekong Subregion malaria vectors. Poster session presentes at: Annual meeting of the American Society of Tropical Medicine and Hygiene; 2014 Nov 2-6; New Orleans 2014.

7. Ouedraogo AL, Bastiaens GJ, Tiono AB, Guelbeogo WM, Kobylinski KC, Ouedraogo A, Barry A, Bougouma EC, Nebie I, Ouattara MS, et al: Efficacy and safety of the mosquitocidal drug ivermectin to prevent malaria transmission after treatment: a double-blind, randomized, clinical trial. Clin Infect Dis 2015, 60:357-365.

8. Chaccour C, Lines J, Whitty CJ: Effect of ivermectin on Anopheles gambiae mosquitoes fed on humans: the potential of oral insecticides in malaria control. J Infect Dis 2010, 202:113-116.

9. Slater H KK, Foy B, Alout H, Churcher T, Bousema T, Ghani A: Ivermectin for malaria control: model validation to existing data and designing trials to detect an impact using clinical and entomological metrics. In 64th Annual meeting of the American Society of Tropical Medicine and Hygiene; 2015 Oct 25-29; Philadelphia

10. Slater HC, Walker PG, Bousema T, Okell LC, Ghani AC: The potential impact of adding ivermectin to a mass treatment intervention to reduce malaria transmission: a modelling study. J Infect Dis 2014, 210:1972-1980.

11. RIMDAMAL: study information available at Clinicaltrials.org. https://clinicaltrialsgov/ct2/show/NCT02509481?term=NCT02509481&rank=1 (Accessed August 2015).

12. Burrows JN, van Huijsduijnen RH, Mohrle JJ, Oeuvray C, Wells TN: Designing the next generation of medicines for malaria control and eradication. Malar J 2013, 12:187.

13. Pacque M, Munoz B, Greene BM, Taylor HR: Community-based treatment of onchocerciasis with ivermectin: safety, efficacy, and acceptability of yearly treatment. J Infect Dis 1991, 163:381-385.

14. White MT, Conteh L, Cibulskis R, Ghani AC: Costs and cost-effectiveness of malaria control interventions--a systematic review. Malar J 2011, 10:337.