1. **Title of the project:** Demonstration of the potential of a single dose malaria cure of artemether-lumefantrine through reformulation in a nano-based drug delivery system

2. **Proponent/s of the project:**
   SA Council for Scientific and Industrial Research (CSIR) (lead investigators); SA Medical Research Council (MRC); Medicines for Malaria Venture (MMV); University of Cape Town and Kenya Medical Research Institute (KEMRI)

3. **Project executive summary**

   Amongst the key unmet needs in malaria treatment is the need for a single dose antimalarial cure; better medicines for uncomplicated malaria; and medicines which are more suitable for vulnerable communities including infants. Artemether (faster acting antimalarial) and lumefantrine (longer acting antimalarial) is a highly efficacious artemisinin based combination therapy (ACT) for malaria; however it has a high pill burden and a food effect. The main limitation is the poor aqueous solubility particularly of lumefantrine, which requires the need for high doses (four tablets taken per dose, twice a day for three days) and fatty foods to improve the absorption of the drugs through the intestinal mucosa and maintain therapeutic efficacy. If artemether-lumefantrine is reformulated within a lipophilic drug delivery system to improve the solubility and absorption of the drugs, it has the potential for a single-dose malarial cure, while negating the food effect. The CSIR together with its key technology partners (including MRC, MMV, and others) propose to collaborate to reformulate artemether-lumefantrine using a lipid-based formulation to improve aqueous solubility of the individual drugs as well as to enable controlled delivery of the drugs over a prolonged period. The proposed partnership will enable extensive formulation work to be conducted, coupled with a standard preclinical developmental package and progression to GMP manufacture, followed by first in man safety and toxicity studies which will be conducted in Africa to demonstrate bioequivalence of a single dose (or reduced dose form) cure. Additionally a number of other late-stage MMV clinical candidates with aqueous solubility issues and/or dissolution limited absorption could also potentially benefit from formulation work. **The primary objective of this demonstrator project is hence to demonstrate the potential of a single-dose cure (or at least a reduced dosage form) for artemether – lumefantrine.** A secondary objective is to reformulate other known antimalarial drugs or late-stage drug candidates into a single-dose injectable to increase the therapeutic outcome. If the single-dose cure or even a reduced dosage form (i.e. one dose per day) for Artemether-lumefantrine proves successful, it could make a big impact with respect to therapeutic outcome since patients are more likely to comply and complete treatment, which could potentially influence mass drug administration for malaria treatment.

4. **Innovative aspects of the project**

   - **Delinkage of the cost of R&D from the final product price** will be achieved by push-funding from various funding sources and equitable technology licencing to ensure access and influence the pricing of the final product.

---

1 The total length of this report should not exceed two pages.
• **Open knowledge innovation to ensure access and collaboration** within the scientific community will be achieved by creation of a data portal to ensure sharing of key scientific data, project status and updates amongst consortium members, and broader community.

• **The intellectual property strategy** will focus on ensuring affordable access for low and middle income countries especially those endemic to malaria.

• **Project IP will be managed to promote accessibility** to the consortium members and formal IP will be filed only in cases where it is believed to be necessary to attract appropriate commercial partners. Equitable licensing strategies will be adopted with the intention of achieving cost-plus pricing of products.

5. **The current status of the project**

The project is before the implementation process. We are currently awaiting an award from WHO based on the recommendation of the Ad Hoc Committee.

6. **Progress towards activities since the start of the project**

We are currently in the process of establishing a project consortium and a technical advisory board for the project. The first project consortium meeting is planned for 25 April in Cape Town.

7. **The first-round award received/expected from WHO based on the recommendation of the Ad Hoc Committee**

Or  The first-round financial support requested (for those projects having not received the recommendation of the Ad Hoc Committee)

We are expecting a financial support of $5 million over 36 months.

8. **Future developments and challenges**

<table>
<thead>
<tr>
<th>Key Tasks</th>
<th>Deliverables</th>
<th>Estimated duration</th>
<th>Budget/$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Formulations</td>
<td>Development of two promising formulations: 1) Reformulated artemether:lumefantrine 2) Reformulated long-acting injectable</td>
<td>8 months</td>
<td>265 000</td>
</tr>
<tr>
<td>2: In vitro studies</td>
<td>In vitro efficacy demonstrated for the formulations based on in vitro biological activity, pharmacokinetics, and toxicity</td>
<td>9 months</td>
<td>150 000</td>
</tr>
<tr>
<td>3. Product development, optimisation and scale-up</td>
<td>Most promising formulations will be developed and optimised into final product. Manufacturing process will be scaled-up</td>
<td>22 months</td>
<td>185 000</td>
</tr>
<tr>
<td>4. Pre-clinical development package</td>
<td>Pre-clinical development package comprising non-GLP and GLP toxicity studies in rats and dogs</td>
<td>24 months</td>
<td>760 000</td>
</tr>
<tr>
<td>5. GMP manufacturing</td>
<td>Most promising formulation will be taken forward for GMP manufacture via a suitable technology partner</td>
<td>6 months</td>
<td>500 000</td>
</tr>
<tr>
<td>6 Clinical studies</td>
<td>Final preclinical dossier will be handed to an identified CRO for Phase I clinical trials</td>
<td>6-9 months</td>
<td>1 600 000</td>
</tr>
<tr>
<td>7. Project coordination, management, and open access</td>
<td>Innovative aspects in place for project management, coordination amongst partners, open access, prize challenges, IP management, licensing</td>
<td>36 months</td>
<td>670 000</td>
</tr>
<tr>
<td><strong>TOTAL</strong> -incl 8% contingency+14% VAT</td>
<td>Demonstration of the potential of a single-dose malarial cure with bioequivalence and 1st in man toxicity studies</td>
<td>36 months</td>
<td>$5 084 856</td>
</tr>
</tbody>
</table>

9. **Other sources of support**

None at this stage

10. **Any additional comments**

-