Standard Template for a Candidate Demonstration Project

Note: the questions with asterisk should be filled.

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.* Submitted by:

Left blank to facilitate impartial evaluation.

3.* Target disease or health condition:
(Focus on type II and III diseases and special R&D needs of developing countries in type I diseases where there is an identified health technology gap.)

Target Disease-Type 1, II and III

4.* The suggested health technology that project seeks to develop:
(e.g. medicine; diagnostic test; medical device; vaccine etc.)

Medicine-application of nanotechnology to improve the effectiveness of currently approved antimalarials (artemether-lumefantrine), and provide a ‘single-dose cure’ from these drugs.

5.* Project summary:

The World Health Organization recommended the use of artemisinin and its derivatives as a partner drug in combination treatments, to replace artemisinin monotherapies in the treatment of uncomplicated malaria. Parasite resistance to artemisinins has now been detected in Cambodia, Myanmar, Thailand and Viet Nam (WHO 2012). However, despite the observed reduction in parasite sensitivity to artemisinins, Artemisinin combination therapies (ACTs) continue to cure patients provided that the partner drug is still efficacious (WHO 2012).

Lumefantrine co-formulated with artemether has been the most widely used ACT. Lumefantrine and arthemeter continue to be efficacious in the treatment of malaria but have been faced with limitations such as poor bioavailability and multiple dosing, hence poor patient compliance. Bioavailability is the fraction of an administered dose of drug that reaches the systemic circulation. When a drug is administered intravenously, the bioavailability is 100%, however this is not the case when administered orally as is the case with the antimalarials in this study. In the
oral route of administration, the drug must first be absorbed in the intestine, and as the drug passes through the intestine and liver, metabolism occurs mainly by the cytochrome P450 (CYP) family of enzymes, (first-pass metabolism) and further excretion may take place thus reducing its bioavailability. Lumefantrine has a poor and erratic absorption with bioavailability of about 57%. Similarly, artemether has recorded poor bioavailability of about 35%. This limited absorption and poor bioavailability necessitates use of larger doses of drug to ensure appropriate plasma concentration. Moreover, any attempt to increase the dose administered to patients in order to augment the therapeutic dose in case of tolerance is likely to cause toxicity.

The primary objective of this study, therefore, is to enhance the oral therapeutic effectiveness of lumefantrine and artemether in combination by entrapping them in nanomedicine drug delivery systems (NMDDS). The NMDDS will be designed in such a way as to improve the drug bioavailability and slowly release and hence enhance the circulatory time of the therapeutic agents in the blood. This may enhance the exposure of the plasmodium parasite to the antimalarials. Currently the two drugs of the fixed dose are taken twice daily for three days. NMDDS presents the ability to achieve single dose therapy. The potency of the drug could be maximised and patient compliance enhanced by reducing dose and dose frequency. Therapeutic agents will be comparatively evaluated in vitro and in a mouse model.

The CSIR nanomedicine platform, a Centre of Excellence in nanomedicine, (COE), has preliminary data with the antimalarial tafenoquine delivered in NMDDS showing significant enhancement in bioavailability and half-life in mice. We plan to develop NMDDS for lumefantrine and artemether, by applying our technology, to enhance bioavailability, increase the circulatory time and maintain therapeutic concentrations for longer periods at the target site.

(Maximum 500 words)

6.* Public health need that the proposed project aims to address:
(Explain the public health need in terms of burden of disease; prevalence; incidence; fatality rate; geographical spread; current interventions and their limitations; and what proposed new technology would change in terms of disease prevention, control, diagnosis, treatment etc. If detailed information is not possible at present then please provide some basic level information)

Malaria is a leading cause of morbidity and death in sub Saharan Africa. About 3.3 billion people which is about half of the world's population are at risk of being infected with malaria (WHO 2012). In 2011, about 99 countries recorded ongoing transmission (WHO 2012), while an estimate of 219 million cases was reported worldwide. Of this number, 174 million (80%) were in Africa. About 98% of malaria cases in Africa are attributable to P. falciparum - the most virulent form of the parasite. In 2010, 660,000 cases of mortality due to malaria were reported globally. In sub-Saharan Africa where more than 90% of morbidity and deaths occur, a child dies of malaria every 12 seconds (Snow et .al., 2005). This death toll exceeds the mortality rate from AIDS and the situation has further been heightened due to concomitant infection of malaria and HIV. Africa spends about 1.2 billion US dollars per year pertaining to malaria-related illnesses and mortality cost (Murray 2006).

Chloroquine (CQ) was the mainstay of malaria treatment for many decades, but development of drug resistance by the parasite led to therapeutic failure. Where resistance to CQ appears,
Sulphadoxine-Pyrimethamine SP usually replaces CQ but often resistance to this drug also rapidly develops. Primaquine, which is a potent prophylactic drug against the liver stage of the disease, has been shown to be prone to adverse events. The World Health Organization has recommended the use of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria. However resistance and hence treatment failures have been recorded in various regions such as Pailin, Cambodia, Mae Sot and Thailand (WHO 2013). The derivatives of artemisinin e.g. artemunate and dihydroartemisinin have poor bioavailability and short half-life. The challenges posed by resistance to current treatment and the difficulties encountered with development of effective vaccine extol the urgent need for development of novel drugs or optimisation of existing antimalarial drugs.

Nanomedicine - the application of nanotechnology in medical treatment, presents the ability to improve the therapeutic properties of current antimalarials. Doxil, a nanomedicine formulation of the anthracycline drug doxorubicin, is used to treat cancer in AIDS-related Kaposi Sarcoma and multiplemyeloma. Our preliminary finding with tafenoquine recorded significant enhancement in bioavailability (from 55% to 99%). We propose to apply our technology in malaria nanomedicine to enhance the shortfalls of artemether and lumefantrine.

(Maximum 400 words)

7.* Explain which new and innovative approaches and mechanisms to supporting financing and coordination of R&D this project would demonstrate?

(This is a very important part to be filled. The idea of these demonstrations projects is “to address identified gaps that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken” (WHA66.22). 66th WHA considered these demonstration projects as part of the efforts to “take forward action in relation to monitoring, coordination and financing for health research and development”. The assembly decided to identify such projects that: “(a) address identified research and development gaps related to discovery, development and/or delivery, including promising product pipelines, for diseases that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken; (b) utilize collaborative approaches, including open-knowledge approaches, for research and development coordination; (c) promote the de-linkage of the cost of research and development from product price; and (d) propose and foster financing mechanisms including innovative, sustainable and pooled funding; (2) The demonstration projects should provide evidence for long-term sustainable solutions.”)

At the core of the challenges faced by Artemether and Lumefantrine is poor drug absorption into the blood stream where the parasite is present and rapid clearance from the blood circulation. The current dose is given two times for three days. A ‘single-dose cure’ for malaria eradication could be achieved via the application of Nanomedicine drug delivery systems (NMDDS).

NMDDS can improve the absorption of the malaria drugs and extend their residence time in the blood, at concentrations sufficient to eradicate the parasite, potentially providing a single-dose cure for uncomplicated malaria. In this demonstration project, we propose that NMDDS can improve the ‘drug properties’ of artemether and lumefantrine and provide a single-dose cure’
from these drugs, which can potentially be taken into clinical trials and translated into the clinic in future.

To achieve this goal we have started discussions to engage stakeholders in the pharma industry namely Novartis who would be partners and mentors in the clinical phase of this project in the next five years as well as the commercialisation of the product. During the 6th MIM conference in Durban South Africa in October 2013, we had a meeting with Novartis who will provide us with artemether and lumefantrine pure compounds for a start. A further detailed strategy to approach Novartis will be determined by consortium members in alignment with the WHO strategy for demonstration projects. We have also held discussions with Medicines for Malaria Venture (MMV). The involvement of a pharma partner and MMV in this project will ensure long term viability and translation of sustainable solutions to the patients. Most of this work is expected to be done through scientific and programme exchange between the CSIR and partner institutes. Our partner institutes such as the University of Cape Town (UCT) have an accredited platform with world class facilities and expertise in malaria in vivo and pharmacokinetic studies for both animal models (Pre-clinical studies) and human beings (Clinical trials). We also have a collaboration with CREATES/KEMRI, MUHAS and AiBST Kenya, Tanzania and Zimbabwe respectively for similar reasons as well. This plan has been put in place in order to share their expertise, apply for additional grants, publish results jointly and attend workshops and conferences where results will be shared and discussed and also build capacity with a multidisciplinary vision in the respective institutions. Very importantly CSIR is committed to staff development, skill enhancement and the provision of an efficient infrastructure and facility for research capacity strengthening. They are also very supportive in payment of staff salaries.

(Maximum 300 words)

8. Evidence of market failure/research landscape:
(Explain why there has been no investment in this technology or why investment has not resulted in access to the health care product.)

The WHO has recommended the use of (ACTs) for the treatment of uncomplicated malaria. However resistance and hence treatment failures have been recorded in various regions such as Pailin, Cambodia, Mae Sot and Thailand (WHO 2013). The challenges posed by resistance to current treatment as well as difficulties encountered with malarial vaccine development places urgent need for either the development of novel drugs or optimizing the use of existing drugs. Nanotechnology is an emerging technology of the 21st century, and has already revolutionized other diseases, e.g. cancer, exemplified by the reformulation of doxorubicin to provide a potent, extended half-life therapy with reduced side effects. Our vision is to see nanomedicine do the same for malaria chemotherapy, radically improving treatment outcomes using currently available drugs, saving lives, and advancing the global goal of eradicating malaria. Investment in nanomedicines by the pharmaceutical industry for poverty related diseases appears to not have been a priority. Part of the reasons is the perceived lack of return on investment, due to the nature of the market and the pricing structures in place for these diseases. One way to mitigate this in this study, is for a research organization such as the CSIR, through a consortium with other African research institutions to provide 'proof of concept' or demonstration of the effectiveness of this technology to achieve the desired therapeutic goals, and then in partnership with 'big pharma' and WHO and MMV to develop the product to translation into the clinic.

(Maximum 200 words)
9. **The scientific and technical feasibility:**

*(Describe the scientific and technical basis for the proposed technology in terms of the state of the art e.g. candidate molecules; biomarkers; pipeline; previous efforts, if any, to develop same or similar technology etc. Include some risk analysis)*

We at the CSIR hold global intellectual property rights to a novel NMDDS platform for infectious diseases (WO2009/15792). Over the past seven years we have successfully applied this platform to improving the effectiveness of drugs used in the treatment of TB. We also envisage low risk owing to balanced international team, track record, previous experience in similar work, complementarity of skills, available equipment, competence of researchers.

Our approach is to develop NMDDS for artemether and lumefantrine, by applying our patented technology, to enhance drug bioavailability, increase the circulatory time and maintain therapeutic concentrations for longer periods at the target site. This may enhance the exposure of the plasmodium parasite to the antimalarials and provide a single dose cure for uncomplicated malaria. Artemether and Lumefantrine can be both encapsulated in polymeric nanoparticles made from lipids. This encapsulation is likely to increase the solubility of these drugs and protect the drugs from degradation in the gastro-intestinal tract. The nanoparticles will also cross the intestinal tract and present the drug into the bloodstream. This will enhance the bioavailability of the drug. Slow release of the encapsulated drug will provide an extension of the half-life of these drugs. The slow release may occur from particles present in the bloodstream or from those sequestered in tissues forming depots. We have conducted preliminary ‘proof of concept’ studies to prove our nanoparticle encapsulation approach. We have determined the impact of nanoparticle encapsulation on tafenoquine (TQ) pharmacokinetics in mice (Figure 1) (data not published). The tafenoquine was encapsulated in a lipidic emulsion. In brief, our results show that the whole blood maximum concentration (Cmax) of TQ is greatly increased when incorporated into the nanoparticles. The observed whole blood concentration showed significant enhancement in the microemulsion formulation of tafenoquine (MTQ), with sizes less than 50 nm. The same was true for the area under the curve (AUC0-inf.). The apparent elimination half-life (t1/2) was 38.3 ± 4.1 hours for the TQ reference formulation and 44.7 ± 1.3 hours for the MTQ, representing approximately a six hour difference between the reference and MTQ. A major improvement in the bioavailability of TQ when incorporated into the nanoparticle formulations was observed. The bioavailability of TQ solution was 55%, and was boosted to 99% from the MTQ.
Figure 1: Mean whole blood concentration versus time graphs following oral administration of free tafenoquine (Reference formulation-FTQ), and tafenoquine micro formulation (MTQ) (thermodynamically stable nanoformulation) in mice (mean ± s.e.m., n = 4).

(More than 500 words)

10. Reasons for proposing:
     (Provide details if any priority setting and/or selection criteria that has underpinned the consideration to take up this area of technology for development.)

Malaria is a leading cause of morbidity and mortality in the developing world. In sub-Saharan Africa morbidity and deaths due to malaria exceed the mortality rate from AIDS and the situation has further been heightened due to concomitant infection of malaria and HIV. Parasite resistance to artemether and lumefantrine used for the treatment of uncomplicated malaria has been reported in South-Asia. At the core of the challenges faced by the Artemether and Lumefantrine are the poor drug properties, i.e. poor drug absorption into the blood stream where the parasite is present and rapid clearance of these drugs from the blood circulation. This gives rise to regimens where increased drug doses are administered over periods of up to three days. Such a regimen presents complexities in its administration, particularly in resource challenged environments. The ‘single-dose cure’ that clinicians and policy makers have called for, as key to successful global malaria eradication could be attained via the application of nanomedicine drug delivery systems (NMDDS).

NMDDS can improve the absorption of artemether and lumefantrine and extend their residence time in the blood, at concentrations sufficient to eradicate the parasite, potentially providing a single-dose cure for uncomplicated malaria.

(Approximately 200 words)
11. **Who could potentially develop the technology/carry out the research?**

(Provide known details: individual researcher? Group of researchers? Research/coordination organization including PDPs? Group of research organizations working together? Combination of these; What would be the process of selection of developers?)

For the demonstration project a consortium will be formed of researchers from the CSIR, CREATE/KEMRI, MUHAS and AIBST.

The CSIR in Pretoria, South Africa will conduct the re-formulation in the drugs in NMDDS. Studies in malaria infected animals will be conducted at UCT and CREATE/KEMRI.

Evaluation of the pharmacokinetic data and parasite elimination data from the animals will be conducted by AIBST, CREATE/KEMRI and MUHAS.

We have started discussions with MMV, and Novartis to form a product development partnership on the basis of the data from the demonstration project. They will greatly assist in taking this work to commercialization. Our platform collaborates extensively with several prestigious academic and research institutions, as well as private companies, nationally and internationally. Most of the consortium and collaborative agreements allow for the sharing equipment/facilities, skills/expertise, laboratory exchange programs, sabbaticals, joint projects and project proposals, co-supervision of students, organizing joint workshops etc.

(Maximum 100 words)

12. **Who could potentially manufacture the final product?**

*Multinational company? Local production? Joint venture? How the decision will be made about the producer?*

The development of the proposed formulation will be developed through the Public Private Partnership model currently facilitated by MMV for the antimalarials. This is why we have engaged MMV early in the concept development. MMV will facilitate the discussion with multinational company for joint venture development since the compounds we are working with are already being manufactured by some companies. MMV will also help the consortium identify other partners to help in the optimization of the lead compounds identified by the current consortium for technical expertise and financial resources.

(Maximum 100 words)

13. **What could be the role of WHO, if any, in this demonstration project to bring this venture to fruition?**

The consortium intends to leverage on WHO for support of this project, both financially, and in brokering the partnerships with the pharmaceutical industry and organizations such as MMV, foundations and bilateral and multilateral partners. The involvement of WHO from the onset of the project is anticipated to support access networks within WHO during all the phases of development, and oversight and monitoring of the project to ensure best science and eventual global implementation of the beneficial aspects of the technology.
14. Please outline a timeframe and projected milestones for the project covering the first 5 years. This should also highlight the immediate actions that need to be taken?

The specific research responsibilities of the Parties will be as follows:

<table>
<thead>
<tr>
<th>Party</th>
<th>Research Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSIR</td>
<td>Manufacturing of nano and micro formulations, support in characterization of formulations, stability of formulations once proof of concept has been illustrated</td>
</tr>
<tr>
<td>Collaborators</td>
<td><em>In vitro</em> cytotoxicity screening of drugs and formulations in human and animal cell lines as well as pharmacokinetic studies, <em>in vitro</em> and <em>in vivo</em> studies</td>
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<td></td>
<td>Joint application of funding and publication</td>
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<td></td>
<td>Joint supervision of students</td>
</tr>
</tbody>
</table>

**PROJECT SCHEDULE**

The estimated schedule for the Project is as described below:

<table>
<thead>
<tr>
<th>Research Products</th>
<th>Start Date</th>
<th>Complete Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation synthesis, optimization and characterization</td>
<td>1 January 2014</td>
<td>31 December 2014</td>
</tr>
<tr>
<td><em>In vitro</em> and <em>in vivo</em> evaluation of drugs singly and in combination using plasmodium parasites and human cell lines</td>
<td>1 January 2015</td>
<td>30 June 2015</td>
</tr>
<tr>
<td>Pharmacokinetic evaluation therapeutic agents in mice</td>
<td>1 July 2014</td>
<td>31 December 2014</td>
</tr>
<tr>
<td>Acute toxicity studies in mice and monkeys</td>
<td>1 January 2015</td>
<td>30 June 2015</td>
</tr>
<tr>
<td><em>In vivo</em> efficacy studies in mice using a plasmodium strain</td>
<td>1 July 2015</td>
<td>31 December 2015</td>
</tr>
</tbody>
</table>
15. What is the intellectual property (IP) landscape relative to this project? Is there any IP, e.g. patents that need to be licensed in to be able to develop and market the product in developing countries? How would IP and related intellectual assets, including knowhow, proposed to be managed in this project?

The team has established a broad portfolio of know-how in the field of nano-sized drug delivery systems extending from liquid state colloidal systems (i.e. nanoemulsion and microemulsion) to semi-solid and solid nanoparticulate systems (e.g. solid lipid nanoparticles, polymeric nanoparticles...) produced by means of various novel and well established encapsulation techniques. These systems have been successfully developed by the team aiming to effectively address the issue of patient non-compliance to treatment in the case of diseases requiring lengthy treatment time periods over months or years (e.g. drug susceptible as well as multidrug resistant TB and HIV). They have been equally applied in an attempt to reverse resistance of anti-malaria drugs such as primaquine and quinine. Furthermore, the team has demonstrated the capability of developing nanocarriers that are able to target and deliver the therapeutic cargo in diseased cells of specific organs with the objective of significantly reducing the dose hence minimising toxic side effects. The team has filed an invention for a novel technique of producing multifunctional polymeric nanocarriers loaded with therapeutic agents and the patent (WO 2009105792 A1) was granted in various territories including the EU, Singapore, in certain African regions and very recently it has received a favorable report of patentability in USA. An
additional invention related to the process of producing colloidal systems for enhanced bioavailability was recently filed for PCT. Several other related invention disclosures were made in the team and are still being investigated for feasibility. The background IP related to the manufacturing of nano-sized delivery systems so far developed at CSIR is managed by the CSIR R&D Outcomes and IP office. The foreground IP that will be developed by the team during the execution of this project will be managed by the consortium. The commercialization strategy will be equally developed by the consortium and partners that will be incorporated during the execution of this program.

(Maximum 400 words)

16.* What would be the strategy to ensure access to the product once it is developed?

(Access is an important dimension of these demonstration projects, it is important for the projects to begin with the end in mind, explain how this project would deliver the technologies to the needy patients i.e. price and affordability; modes of supply; storage; prescription; dispensing; and compliance; WHO will develop guiding principles for ensuring access to any products coming out of the demonstration projects)

The development of this product will occur as part of a public-private partnership between the African research institutions and pharma facilitated by organizations such as MMV and WHO. Affordable access of this product is important, and the goal is to develop the product at a $1 a day treatment cost. The technology to be implemented is a simple encapsulation of the drug, and is readily scalable. The technology will be transferred to pharmaceutical companies for scale up and clinical development. The product is intended to be rolled out at cost from the pharmaceutical companies. Precedent have already been set by MMV in the development of new antimalarials (dispersible Coartem, Eurartesim, Pyramax), Malaria Vaccine Initiative (MVI) in the development of malaria vaccine RTS, and DNDi (ASAQ, ASMQ). Similar negotiations for this product with pharma is anticipated to ensure affordable access to this product.

(Maximum 400 words)

17. How could the project be financed paying particular attention to the need to demonstrate new and innovative forms of financing? Also provide an estimated cost of the project.

We hope to be funded by WHO, our employers will take care of our salaries and some in-kind support such as infrastructure, equipment, overhead costs and human capital development. The project will be in accordance with the guiding principles between South Africa, Kenya, Tanzania, Zimbabwe and WHO. Once we have an optimized lead candidate molecule, MMV will play a key role in discussion with pharma partners within their current
framework. The consortium partners in collaboration with MMV will mobilize resources to support the clinical development costs for the product. We envisage that some of the costs may be covered by our governments or prior funding for infectious disease drug development.

(Maximum 200 words)
## Estimated cost of project activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Estimated cost</th>
<th>Start Date</th>
<th>Complete Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation synthesis, optimization and characterization</strong>&lt;br&gt;Cost for consumables for formulation, optimization and characterization <strong>20 000 USD</strong></td>
<td>1 January 2014</td>
<td>31 December 2014</td>
<td></td>
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<tr>
<td><em>In vitro and in vivo evaluation of drugs singly and in combination using plasmodium parasites and human cell lines</em>&lt;br&gt;Cost for consumables to investigate activity in sensitive and resistant strains of Plasmodium parasites and for selectivity studies <strong>14 500 USD</strong></td>
<td>1 January 2015</td>
<td>30 June 2015</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacokinetic evaluation</strong>&lt;br&gt;<strong>therapeutic agents in mice</strong>&lt;br&gt;PK study in 6 mice that includes LC/MS/MS estimation of 1 or 2 analytes (<strong>5 500 USD</strong>)</td>
<td>1 July 2014</td>
<td>31 December 2014</td>
<td></td>
</tr>
<tr>
<td><strong>Acute toxicity studies in mice and monkeys</strong>&lt;br&gt;<em>Toxicokinetics in mice (10 000 USD) and monkeys (30 000 USD)</em></td>
<td>1 January 2015</td>
<td>30 June 2015</td>
<td></td>
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<tr>
<td><em>In vivo efficacy studies in mice using a plasmodium strain</em>&lt;br&gt;<em>Exposure analysis for PK/PD evaluations and efficacy studies (30 000 USD)</em></td>
<td>1 July 2015</td>
<td>31 December 2015</td>
<td></td>
</tr>
<tr>
<td>Project Description</td>
<td>Exposure Levels</td>
<td>Start Date</td>
<td>End Date</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
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</tr>
<tr>
<td><em>In vivo</em> efficacy studies in mice using two Plasmodium strains</td>
<td><em>exposure levels x 2</em></td>
<td>1 January 2016</td>
<td>30 April 2016</td>
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<tr>
<td></td>
<td>(10 000 USD) efficacy studies in mice</td>
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<tr>
<td></td>
<td>25 000 USD</td>
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<tr>
<td><em>In vivo</em> prophylactic and curative evaluation of the selected therapeutic agents at different doses when used in combination in mice</td>
<td><em>exposure levels for PK/PD studies</em></td>
<td>1 January 2016</td>
<td>31 December 2016</td>
</tr>
<tr>
<td></td>
<td>(10 000 USD) efficacy studies for prophylactic and curative drug evaluation in mice</td>
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<tr>
<td></td>
<td>(50 000 USD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data and results compilation</td>
<td></td>
<td>1 October 2016</td>
<td>30th January 2017</td>
</tr>
<tr>
<td><em>In vivo</em> pharmacokinetic studies of therapeutic agents in monkeys</td>
<td>Exploratory small molecule PK study in 6 rhesus monkeys; includes LCMS analysis</td>
<td>1 February 2017</td>
<td>30 June 2017</td>
</tr>
<tr>
<td></td>
<td>(20 000 USD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>In vivo</em> prophylactic and curative evaluation of the selected therapeutic agents at different doses when used in combination in monkeys</td>
<td>Exposure levels for PK/PD modeling – (20 000 USD) efficacy studies for prophylactic and curative drug evaluation in monkeys</td>
<td>1 July 2017</td>
<td>30 June 2018</td>
</tr>
<tr>
<td></td>
<td>60 000 USD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data and results compilation and publication</td>
<td></td>
<td>1 Jul 2018</td>
<td>1 Jan 2019</td>
</tr>
</tbody>
</table>

*Exploratory toxicokinetics studies with single and repeated dose toxicity studies. The study is performed at four dose levels (vehicle, low, mid and high) and each dose level comprised of 3-6 male and 3-6 female animals. Animals are dosed daily (OD/BID) for 1/7/14/28 consecutive days via one of route of administration (PO) the route intended for
Blood are collected at 6-9 time points over 24-72 hours on day first and day last of dosing. A bioanalytical procedure for measuring the concentration of test substance and its possible metabolites is developed and samples are assayed by LC-MS/MS. All toxicokinetics parameters are calculated using WinNonLin Software. Post PK/PD and toxicity evaluation is the efficacy studies in mice and monkeys to comparatively evaluate the therapeutic efficacy of formulated and unformulated antimalarials in challenged animals.

The total cost for the *in vitro* and *in vivo* antiplasmodial investigation, PK evaluation, toxicokinetics, PK/PD in mice and monkeys are estimated at about 310 000 USD.

**18. How could the project be governed and coordinated paying particular attention to the need to demonstrate better way of coordination?**

We have already an ongoing collaboration which has given birth to consortium working on the nanomedicine for malaria.

The Council for Scientific and Industrial Research (CSIR) will act as the project secretariat and the integrative point of responsibility for this platform. Electronic mails and phone calls will be used as appropriate. Progress report update among members/collaborators will be discussed monthly via teleconferences and an annual meeting will be instituted where members will convene at a chosen venue to discuss progress and a way forward. Financial management will be under the secretariats auditing requirements. The CSIR is widely recognised for its strong corporate governance and receives a clean audit from the South African Auditor-General every year. The partners involved in this program are already working as a consortium and already have a good working relationship leveraging on the diverse complementary expertise that each group bring onto the platform.

*(Maximum 200 words)*

**19. Have any donor agencies/governments already indicated interest in supporting the project?**

The South African, Kenyan and Tanzanian governments have been supporting this initiative. This has been through the South African/Kenya and South African/Tanzania science and Technology partnership which involves both governments contributing equally to support a project. The Consortium for National Health Research (CNHR) of Kenya is also support the post-doctoral fellowship on the antimalarial nano-formulation.

*(Maximum 200 words)*