APPLICATION FOR INCLUSION OF

DIHYDROARTEMISININ PLUS
PIPERAQUINE (DHA/PPQ)

FIXED DOSE COMBINATION TABLETS
IN THE 17th EDITION OF THE WHO MODEL
LISTS OF ESSENTIAL MEDICINES
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<th>Description</th>
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<tr>
<td>ACT</td>
<td>Artemisinin Combination Treatment</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AMF-m</td>
<td>Affordable Medicine Facility-malaria</td>
</tr>
<tr>
<td>A/L</td>
<td>Artemether/Lumefantrine</td>
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<tr>
<td>AS/AQ</td>
<td>Artesunate - amodiaquine</td>
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<tr>
<td>AS+MQ</td>
<td>Artesunate plus mefloquine</td>
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<tr>
<td>AS+SP</td>
<td>Artesunate plus sulfadoxine–pyrimethamine</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DHA</td>
<td>Dihydroartemisinin</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>FCT</td>
<td>Fever clearance time</td>
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<tr>
<td>FDC</td>
<td>Fixed-Dose Combination</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>ITT</td>
<td>Intention-To-Treat</td>
</tr>
<tr>
<td>Kcal</td>
<td>Kilo-calorie</td>
</tr>
<tr>
<td>MMV</td>
<td>Medicines for Malaria Venture</td>
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<tr>
<td>PCT</td>
<td>Parasitaemia clearance time</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
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<tr>
<td>PPQ</td>
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<tr>
<td>P. falciparum</td>
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<td>QTc</td>
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<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>STEAE</td>
<td>Serious Treatment-Emergent Adverse Event</td>
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<tr>
<td>TEAE</td>
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</tr>
<tr>
<td>TF</td>
<td>Treatment failure</td>
</tr>
<tr>
<td>USD</td>
<td>United States Dollar</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1. Summary Statement of the Proposal for Inclusion

Malaria remains a major cause of morbidity and death in endemic areas and substantial numbers of travelers from non-endemic areas are exposed to the risk of malaria each year.

The most severe form of malaria, which is responsible for the great majority of malaria-related deaths (most of which occur in children aged < 5 years who reside in endemic areas), is associated with infection due to the species *Plasmodium falciparum* (*P. falciparum*). Of the four *Plasmodium* species that infect man *P. falciparum* has the shortest exo-erythrocytic phase (7-10 days) and the merozoites released after asexual reproduction of sporozoites in hepatic cells are able to invade erythrocytes at any stage of their development.

Because of the relentless increase in resistance of *P. falciparum* to drugs such as chloroquine, sulfadoxine–pyrimethamine and mefloquine, new agents have had to be developed. The World Health Organization (WHO) has recommended that artemisinin combination treatment (ACT) should be regarded as the “policy standard” for treatment of malaria in areas where *P. falciparum* is the predominant infecting species. In developing ACT regimens the aim is to achieve rapid schizontocidal activity by means of the selected artemisinin compound together with a longer antimalarial effect associated with the different mechanism of action and longer half-life of the selected partner agent.

The latest version (16th ed., updated March 2010) of the WHO Model Essential Medicines List states that it “currently recommends combinations according to treatment guidelines.” Currently, the only fixed-dose combination (FDC) ACT included in the 16th edition is artemether + lumefantrine.

It is noteworthy that the 2nd edition of WHO’s Guidelines for the Treatment of Malaria (March 2010) expanded to include one additional FDC, dihydroartemisinin plus piperaquine (DHA/PPQ), as an ACT option for the “first-line treatment of uncomplicated *P. falciparum* malaria worldwide”. This addition was categorized as a “Strong Recommendation” and was included due to “High Quality Evidence.”

This proposal for inclusion of DHA/PPQ seeks to harmonize the recommendations of the Technical Guidelines Development Group for WHO’s Guidelines for the Treatment of Malaria with the future recommendations of the WHO Expert Committee on the Selection and Use of Essential Medicines, by recapitulating the evidence reviewed and justifying the use of DHA/PPQ as an efficacious, safe and cost effective medicine for the treatment of uncomplicated *P. falciparum* malaria.

Comparative benefits: As a once-a-day FDC taken over the course of three days, DHA/PPQ will offer a simpler dosing burden for patients compared to the pill burden of twice-per-day treatment over three days for artemether+lumefantrine. This diminished burden will benefit patients and enhance the likelihood of improved treatment compliance in settings where patients are administered treatment with limited or no medical oversight. In addition, the longer half-life of this companion non-artemisinin component compared to Coartem’s (piperaquine vs lumefantrine) confers longer patient protection from reinfection, a critical consideration in areas of high malaria transmission.

Today, there is no WHO-prequalified version of DHA/PPQ available. However, sigma-tau’s application for EMA approval of its version of DHA/PPQ (*Eurartesim*®) has been under stringent regulatory review since July 2009 and a final favorable opinion is expected in Q1 2011. WHO
prequalification should be obtainable within the first half of 2011. As such, by the time of the final decision of the WHO Essential Medicine List Expert Committee, a safe, efficacious, WHO-pre-qualified version of DHA/PPQ should be available for use worldwide.

As of today, there are two countries that have officially listed DHA/PPQ as their national first-line treatments following WHO’s guideline recommendation: Vietnam and Cambodia. In addition, the case of Cambodia is exceptional: it is the only SE Asian country invited to participate in the Phase One rollout of the Affordable Medicines Facility-malaria, and the country has insisted on the critical role of DHA/PPQ as a subsidized ACT distributed via the private sector, in order to drive out sales of sub-standard or co-blistered artemisinin-based products.

Other countries have included DHA/PPQ as an additional or alternative first-line treatment in their national guidelines (Ghana, Nigeria), and many others have indicated an interest in doing so in the future when a WHO pre-qualified version becomes available.

Safety and Efficacy Data

The development of *Eurartesim* builds on the available experience with *Artekin*, a DHA/PPQ product first approved in China and subsequently studied and approved for use in several countries in SE Asia, where multi-drug resistant *P. falciparum* infections are common. The manufacture of Eurartesim is carried-out using the most current GMP standards, including the possible genotoxic potential of the active ingredients, their metabolites and the final degradation products. Otherwise, Eurartesim is similar to Artekin, so that pharmacokinetic, safety and efficacy data generated with one formulation can be extrapolated to the other.

Summary of the Efficacy Data

DHA/PPQ has been tested in two Phase III clinical trials conducted by Sigma-tau in patients with *P. falciparum* malaria. The first one was conducted in children and adult Asian patients and the second one in African children (≥6 months, ≤5 years).

The Asian Phase III (Valecha N et al., 2010) trial was a randomised, active-controlled, non-inferiority trial, to assess the efficacy and safety of DHA/PPQ in comparison with *Artesunate+Mefloquine* (AS+MQ) in children and adult patients affected by uncomplicated *P. falciparum* malaria. A total of 769 patients received DHA/PPQ and 381 AS+MQ. Results in the two co-primary populations for analysis showed a Day 63 PCR-corrected cure rate of 97.0% for DHA/PPQ and 95.3% for AS+MQ (modified-Intention-To-Treat, m-ITT, population) and 98.7% for DHA/PPQ and 97.0% for AS+MQ (Per Protocol, PP, population), demonstrating similar good results in terms of efficacy for both the two treatments. In addition, the analysis of the 63 days of follow up showed that DHA/PPQ significantly reduced the risk of new infections (Kaplan-Meier estimates of the proportions of patients with new infections on day 63 were 22.7% for DHA/PPQ and 30.3% for AS+MQ, ITT population).

The African Phase III trial (Bassat Q et al., 2009) was carried out in children affected by uncomplicated *P. falciparum* malaria. The study was designed as a randomised, active-controlled, non-inferiority trial, to assess the efficacy and safety of DHA/PPQ in comparison with *Artemether/Lumefantrine* (A/L, Coartem®).
The randomized population consisted of 1039 children treated with DHA/PPQ and 514 with A/L. The results showed a Day 28 PCR-corrected cure rate of 92.7% for DHA/PPQ and 94.8% for A/L (m-ITT population) and of 95.7% for both DHA/PPQ and A/L (PP population). The study demonstrated that both ACTs had similar efficacy to cure uncomplicated \textit{P. falciparum} malaria. In addition, the analysis of the 42 days of follow up showed that DHA/PPQ significantly reduced the risk of new infections (Kaplan-Meier estimates of the proportions of patients with new infections on day 42 were 13.6% for DHA/PPQ and 24.0% for A/L, ITT population). This effect is attributable to the long half life of PPQ and is expected to have a major impact to improve the health care system of the countries were malaria is endemic.

Efficacy data have been also collected in two pharmacokinetics trials carried out in patients with uncomplicated \textit{P. falciparum} malaria. One trial was carried out in Burkina Faso, where 32 children (\(\geq\)1 year, \(\leq\)5 years) have been treated with DHA/PPQ. The Day 28 PCR-corrected cure rate was 87.5% in the ITT population and 93.3% in the PP population. A similar PK trial was carried out in Thailand, where 25 adult patients with uncomplicated \textit{P. falciparum} malaria have been treated with DHA/PPQ. The Day 90 PCR-corrected cure rate was 100% in the ITT population.

Similar good results have been obtained with DHA/PPQ in many other clinical studies reported in literature (see section 10).

It can be concluded that treatment with DHA/PPQ for uncomplicated \textit{P. falciparum} malaria is effective.

**Summary of Safety Data**

In the Asian phase III study, the proportion of patients experiencing at least one treatment-emergent adverse event (TEAE) was slightly lower in the DHA/PPQ group compared with the AS+MQ group; 69.4% (DHA/PPQ) vs. 72.4% (AS+MQ). The most frequently reported TEAEs (related and unrelated) in the DHA/PPQ and AS+MQ groups, respectively, were headache (18.9% vs. 20.7%), malaria (14.5% vs. 22.6%), \textit{P. falciparum} malaria (13.4% vs. 15.2%) and pyrexia (10.6% vs. 11.3%). The adverse event profiles for both DHA/PPQ and AS+MQ were similar in terms of type and frequency of adverse events (AE). There were 12 serious TEAEs (1.6%) in the DHA/PPQ group and three serious TEAEs (0.8%) in the AS+MQ group, including one case of encephalitis that was probably related to MQ. There were no deaths.

At enrolment patients were mildly thrombocytopenic and showed signs of haemolysis. During the study laboratory changes were consistent with recovery from malaria.

Mild QTc interval prolongation was reported as a TEAE in 5.4% (DHA/PPQ) vs. 4.2% (AS+MQ) patients. The change in QTc from baseline to Day 2 between treatments was statistically significant; by Day 7, the QT prolongation was completely resolved.

In the African phase III study, the proportion of patients experiencing at least one TEAE was similar between treatment groups; 79.3% (DHA/PPQ) vs. 80.6% (A/L). Pyrexia (29.1% vs. 32.0%) and \textit{P. falciparum} infections (19.0% vs. 25.9%) were reported more frequently in the Coartem group. The adverse event profile for both DHA/PPQ and A/L was very similar in terms of type and frequency of events and was consistent with malaria expectations. There were similar STEAEs in the DHA/PPQ group compared with the Coartem group; 1.7% vs. 1.0% (\(p = 0.249\)), respectively, as were also the related STEAEs: 1.5% vs. 0.8% (\(p = 0.332\)). There were two deaths in the study, one in the DHA/PPQ group (judged unlikely related to study treatment by the investigator), and one in the Coartem group (judged possibly related by the investigator).
At recruitment, patients were anaemic and mean platelet counts were at the lower end of the normal range. The anaemia and platelet counts improved and a mild eosinophilia was observed, particularly in the A/L-treated group.

Mild QTc prolongation (all preferred terms) was reported as a TEAE by 26 (2.5%) DHA/PPQ-treated and 13 (2.6%) Coartem treated patients in the study. No arrhythmias were reported during the study.

Following the results of the phase III studies, a study properly designed for addressing the QTc prolongation has been carried-out. This study has shown that the prolongation in QTc observed at the end of the treatment with Eurartesim administered with a high or a low Kcal diet is significantly reduced when the drug is administered in fasting conditions with water.

The safety and efficacy of Eurartesim in children aged <6 months and in children weighing <5kg has not yet been evaluated. No data are available for these paediatric subsets.
2. Name of the Focal Point in WHO Submitting or Supporting the Application

Dr. Peter Olumese, WHO Global Malaria Programme Medical Officer
3. Name of the Organisation(s) Consulted and/or Supporting the Application

Medicines for Malaria Venture (MMV), Geneva, Switzerland (see attached letter of support by MMV’s CEO Dr. Dennis Schmatz).

Mahidol-Oxford Tropical Medicine Research Unit (see attached letter of support by Prof. Nick White).
4. International Non-proprietary Name (INN, generic name) of the Medicine

Dihydroartemisinin (DHA) and Piperaquine Tetraphosphate (PPQ)

ATC Codes:  
DHA  P01BE05  
PPQ  P01BA
5. Formulation Proposed for Inclusion

Film-coated tablets of a fixed-dose combination of:

- Dihydroartemisinin (DHA)
- Piperaquine (PPQ), as tetraphosphate

Two strengths are proposed for the above formulation:

- 40 mg DHA + 320 mg PPQ
- 20 mg DHA + 160 mg PPQ

A third strength (10 mg DHA + 80 mg PPQ) is being developed for infants in an age-appropriate formulation.
6. International Availability – Sources, if Possible Manufacturers

As of the date of this submission, there are no WHO pre-qualified manufacturers of DHA/PPQ.

Sigma-tau is the only manufacturer of this product to have submitted a registration dossier for stringent regulatory authority approval (EMA, July 2009). With its partner MMV, Sigma-tau has committed to submitting the product for WHO pre-qualification immediately upon securing EMA approval (expected in Q1, 2011).

DHA/PPQ is also manufactured by Holley-Cotec Pharmaceuticals Company (Guangzhou, China). To-date, this version of the product has not achieved WHO pre-qualification.

Given the significant demand that exists in many African and Asian malaria endemic countries for DHA/PPQ, it is expected that once a version of the product is pre-qualified, generic manufacturers will develop bioequivalent versions for review by WHO’s pre-qualification program.
7. Whether Listing is Requested as an Individual Medicine or as an Example of a Therapeutic Group

DHA/PPQ will be listed as an individual medicine.
8. Information Supporting the Public Health Relevance (Epidemiological Information on Disease Burden, Assessment of Current Use, Target Population)

Epidemiology

Malaria is a widespread disease, endemic in tropical and subtropical climates. It is caused by protozoan parasites of the genus *Plasmodium* which are transmitted by infected bites of the *Anopheles* mosquitoes. There are 4 species of *Plasmodium* capable of infecting humans (*P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*).

*P. falciparum* malaria is the most common and deadly form of the disease. It is estimated to affect more than 500 million people annually and to pose a health risk to up to 2.4 billion people. It has been judged by the WHO to be the direct cause of more than 1 million deaths annually and to pose the single greatest morbidity and mortality burden in children. There were an estimated 881 000 (610 000–1 212 000) deaths worldwide in 2006, of which 90% were in the African Region, and 4% in each of the southeast Asia and Eastern Mediterranean regions (WHO 2008).

One hundred and nine countries were endemic for malaria in 2008, 45 within the WHO African region (WHO 2008). While malaria is considered a rare disease in EU, it is endemic throughout the tropics. Data from the WHO Global Burden of Disease programme probably markedly underestimate the true prevalence of the disease, especially outside Africa, since those estimates were derived from passive reporting. Based on active case-detection studies combined with estimates of populations at risk, a conservative estimate was made of 300-660 million attacks during 2002 (Snow *et al*. 2005). Of these, almost one-third were outside Africa, the majority in southeast Asia, which has the most drug resistant malaria parasites of anywhere in the world (Hien *et al*. 2004).

The prevalence of malaria in the European Union (EU) is almost exclusively the result of disease importation resulting from travel to endemic areas. Total reported malaria cases in EU countries were 8,210 in 2007 (data from WHO website: http://data.euro.who.int/cisid/?TabID=207120).

The global impact of malaria is massive, with direct and indirect harms for patients, their families and societies as a whole. As noted by Sachs and Malaney (2002) "where malaria prospers most, societies have prospered least", with malaria impacting on “fertility, population growth, saving and investment, worker productivity, absenteeism, premature mortality and medical costs”.

The risk of malaria transmission is much greater than in the past, particularly as a result of travel to and from endemic regions (WHO 2006a). It is noteworthy that the clinical picture in malaria is influenced markedly by the pattern and intensity of malaria transmission in the area of residence, which then determines the degree of protective immunity acquired by an individual and in turn, the clinical disease profile.

Current use

Historically, malaria was treated by drug monotherapy, most notably with chloroquine, which was the standard treatment for more than 50 years. Unfortunately, drug resistance developed and is now highly prevalent in nearly all endemic regions. Resistance has been reported to most anti-malarial drugs except for ACT.
Current antimalarial therapy simultaneously employs two or more blood schizontocidal drugs with independent modes of action. This improves therapeutic efficacy and also delays the development of resistance to the individual components of the combination.

To combat the development of resistance, WHO has recommended that monotherapy be eliminated and that malaria should be treated with a combination of an artemisinin derivative and another anti-malarial with a different mechanism of action. This is referred to as ACT. Artemisinin derivatives rapidly decrease the parasite biomass, while the presence of a second anti-malarial with a different mechanism of action reduces the probability of the emergence of resistant strains. WHO encourages the development of FDC versions of ACTs, vs co-blistered presentations which can be misused to facilitate de-facto the monotherapy use of artemisinin.

Five specific ACTs have been recommended over time by the WHO; they are listed in alphabetical order:

- **Artemether - lumefantrine (A/L, Coartem, Novartis)**: it is a FDC approved in several European countries and the United States. A/L is recommended as the first line treatment in a number of African countries, as well as in some Asian and South American countries (WHO, 2006c: Facts on ACTs). Currently, it is the only fixed-dose combination ACT included in the 16th edition of the WHO Model Essential Medicines List.

- **Artesunate - amodiaquine (AS/AQ)**: it’s a FDC manufactured by Sanofi-Aventis, (“Coarsucam” or “ASAQ Winthrop”), which has not been approved by a stringent regulatory authority. It is used as the first line treatment in some African countries, although there is considerable resistance to amodiaquine in the East (but not West) Africa.

- **Artesunate - mefloquine (AS/MQ)**: a FDC is manufactured by Farmaguinhos/DNDi, with tech transfer to Cipla, but has neither obtained stringent regulatory approval nor WHO pre-qualification. It is the first line treatment for uncomplicated *P. falciparum* malaria in Cambodia (until Dec 2010, after which the country will switch to DHA/PPQ), Thailand, Laos, Bolivia, Peru and Venezuela. The safety and tolerability data at the recommended dose (25 mg/kg) were deemed insufficient to support the use of MQ combinations for children in Africa (WHO, 2006).

- **Artesunate + sulfadoxine–pyrimethamine (AS+SP)**: it is only co-blistered, no FDC version is available nor is in development). It is not approved in Europe or the United States. SP resistance is fairly widespread across sub-Saharan Africa and much of the rest of the world.

- **Dihydroartemisinin – piperaquine (DHA/PPQ)**: it was submitted to the European Medicines Agency (EMA) for European approval in July 2009. It is noteworthy that the 2nd edition of WHO’s Guidelines for the Treatment of Malaria (March 2010) expanded to include DHA/PPQ as an ACT option for the “first-line treatment of uncomplicated *P. falciparum* malaria worldwide”. This addition was categorized as a “Strong Recommendation” and was included due to “High Quality Evidence.”

The choice of therapy is influenced by local parasite susceptibility as well as by cost considerations, even though recent data have shown that the use of effective therapy leads to overall cost-benefits (Whiteman *et al* 2006).

**Target population**

The target population for treatment with Eurartesim includes infants aged six months or more (and with a body weight of at least 5 kg), children and adults.
Eurartesim has not been evaluated in patients with severe renal or hepatic impairment. In addition, clinical studies of Eurartesim did not include subjects aged 65 years and over or weighing more than 100 kg. Caution is needed when administering Eurartesim to these patients.
9. Treatment Details (Dosage Regimen, Duration; Reference to Existing WHO and Other Clinical Guidelines; Need for Special Diagnostic or Treatment Facilities and Skills)

**Proposed indication**
Eurartesim™ is indicated for the treatment of symptomatic, uncomplicated *P. falciparum* malaria in adults, children and infants ≥ 6 months and/or ≥5 kg. Appropriate guidelines should be followed when treating malaria.

**Proposed posology and method of administration**
Eurartesim™ is a FDC formulated as tablets for oral administration.

Eurartesim™ should be taken with water without food. For patients unable to swallow the tablets, such as infants and young children, Eurartesim may be crushed, mixed with water and administered as slurry.

If a patient vomits within 30 minutes of taking Eurartesim™, the whole dose should be readministered; if a patient vomits within 30-60 minutes, half the dose should be readministered.

**Dosage**
Eurartesim can be administered to adults, children and infants ≥ 6 months. Dosing should be based on body weight as shown in the table below:

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Daily dose (mg)</th>
<th>Tablet strength and number of tablets per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPQ</td>
<td>DHA</td>
</tr>
<tr>
<td>5 to &lt;7</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>7 to &lt;13</td>
<td>160</td>
<td>20</td>
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<tr>
<td>13 to &lt;24</td>
<td>320</td>
<td>40</td>
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<tr>
<td>24 to &lt;36</td>
<td>640</td>
<td>80</td>
</tr>
<tr>
<td>36 to &lt;75</td>
<td>960</td>
<td>120</td>
</tr>
<tr>
<td>75 to 100</td>
<td>1,280</td>
<td>160</td>
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<tr>
<td>&gt;100</td>
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</tbody>
</table>

If a dose is missed, it should be taken as soon as realised and then the regimen continued until the full course of treatment has been completed.

Per WHO’s 2nd edition Standard Treatment Guidelines, DHA/PPQ should be administered as follows:

“7.5.5 Dihydroartemisinin plus piperaquine
This is currently available as a fixed-dose combination with tablets containing 40 mg of dihydroartemisinin and 320 mg of piperaquine.

**Therapeutic dose.** A target dose of 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperaquine once a day for 3 days, with a therapeutic dose range between 2–10 mg/kg/day dihydroartemisinin and 16–26 mg/kg/dose piperaquine”

No special diagnostic or treatment facilities or skills are needed.
10. Summary of Comparative Effectiveness in a Variety of Clinical Settings

Efficacy results

A total of eight clinical studies have been conducted by Sigma-tau in humans using DHA/PPQ. All of them were compliant with the requirements of the most stringent regulatory authorities. Among them, six were PK studies to investigate the DHA and PPQ pharmacokinetics and the safety of the product and two were phase III trials to demonstrate efficacy and safety of DHA/PPQ in adults and children suffering from acute, uncomplicated *P. falciparum* malaria. Out of the six PK studies, two were conducted in patients (so also efficacy and safety data were obtained in these studies) and four in healthy volunteers.

Both the Phase III studies were designed as open-label, randomized, active-controlled studies to demonstrate the non-inferiority of DHA/PPQ in terms efficacy and safety toward the standard reference therapy which currently is AS+MQ in South East Asia and A/L (Coartem™, Novartis) in Africa.

The primary objective of both the phase III studies was to demonstrate that the PCR-corrected cure rate of DHA/PPQ is non-inferior to that of the comparator. The non-inferiority margin was set at 5%. This margin was tight so that only a very small loss of efficacy was allowed in comparing the new treatment with the reference one.

The African study was focused on monoinfections from *P. falciparum*, while the Asian study allowed also enrolment of patients with mixed infections, i.e. *P. falciparum* and other forms of *Plasmodia*. This difference is justified on the basis of a different epidemiology of malaria in the two countries.

Phase III Asian Study

This study enrolled both male and female, adult and paediatric patients aged between 6 months and 62 years inclusive with a body weight of at least 5 kg and who had microscopically confirmed *P. falciparum* malaria or mixed infection and a history of fever (temperature at $\geq 37.5^\circ C$).

A total of 1150 patients were randomised in the study, according to an allocation ratio of 2:1 in favour of the DHA/PPQ group. The dosing regimen was based on body weight as reported above. AS and MQ were used in accordance with WHO policy for ACT.

The primary efficacy endpoint was the PCR-corrected cure rate at Day 63. The secondary efficacy endpoints of the study were as follows:

- PCR corrected cure rates at Days 28 and 42
- Uncorrected cure rates at Days 28, 42, and 63
- Proportion of patients with treatment failure (TF) as defined by WHO
- Proportion of aparasitaemic patients and time to parasitaemia clearance (PCT)
- Proportion of afebrile patients and time to fever clearance (FCT)
- Proportion of patients with gametocytes

The treatment comparison as for the safety profile was an important goal of the study (safety results are described in section 11).
Efficacy analyses were performed on the pure Intention-To-Treat population (ITT, defined as all randomised patients who received at least one dose of the study treatment), modified ITT population (m-ITT, defined as the pure ITT population with the exclusion of those patients lost-to-follow up for unknown reasons before Day 63) and the Per Protocol population (PP, defined as all randomised patients who showed no major protocol violations).

The m-ITT and the PP populations were chosen as co-primary populations for analysis. Safety analyses were performed on the Safety Population, which was the same as the ITT.

Demographic characteristics of the study population are summarised in the table below.

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>DHA/PPQ</th>
<th>AS+MQ</th>
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<tbody>
<tr>
<td></td>
<td>Safety &amp; Pure-ITT</td>
<td>m-ITT</td>
</tr>
<tr>
<td>N</td>
<td>767 (100%)</td>
<td>726 (95.39%)</td>
</tr>
<tr>
<td>Males</td>
<td>582 (76.43%)</td>
<td>549 (75.62%)</td>
</tr>
<tr>
<td>Females</td>
<td>185 (23.57%)</td>
<td>177 (24.38%)</td>
</tr>
<tr>
<td>Mean Age (Years)</td>
<td>25.44</td>
<td>25.39</td>
</tr>
<tr>
<td>Median Age (Years)</td>
<td>24.83</td>
<td>24.80</td>
</tr>
<tr>
<td>Age Range (Years)</td>
<td>0.68-61.58 (100%)</td>
<td>0.68-61.58 (100%)</td>
</tr>
<tr>
<td>Race: Asian</td>
<td>767 (100%)</td>
<td>726 (100%)</td>
</tr>
<tr>
<td>Mean Weight (kg)</td>
<td>44.34</td>
<td>44.08</td>
</tr>
<tr>
<td>Median Weight (kg)</td>
<td>49.00</td>
<td>49.00</td>
</tr>
<tr>
<td>Weight Range (kg)</td>
<td>6.50-90.00</td>
<td>6.50-90.00</td>
</tr>
</tbody>
</table>

The PCR-corrected cure rates at Day 63 are summarised in the table below.
PCR-corrected and uncorrected cure rates at Day 63 in the Phase III Asian study

<table>
<thead>
<tr>
<th>Study Population (n)*</th>
<th>Cure Rate</th>
<th>DHA/PPQ</th>
<th>AS+MQ</th>
<th>Treatment Difference (DHA/PPQ - AS+MQ)</th>
<th>Lower Limit of one-sided 97.5% CI</th>
<th>Chi-square test, p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>∆</td>
</tr>
<tr>
<td>Pure-ITT (n=767, 381)</td>
<td>PCR-corrected</td>
<td>674</td>
<td>87.87</td>
<td>330</td>
<td>86.61</td>
<td>1.26%</td>
</tr>
<tr>
<td></td>
<td>Uncorrected</td>
<td>516</td>
<td>67.28</td>
<td>227</td>
<td>59.58</td>
<td>7.70%</td>
</tr>
<tr>
<td>m-ITT (n=726, 361)</td>
<td>PCR-corrected</td>
<td>704</td>
<td>96.97</td>
<td>344</td>
<td>95.29</td>
<td>1.68%</td>
</tr>
<tr>
<td></td>
<td>Uncorrected</td>
<td>516</td>
<td>71.07</td>
<td>227</td>
<td>62.88</td>
<td>8.19%</td>
</tr>
<tr>
<td>PP (n=668, 336)</td>
<td>PCR-corrected</td>
<td>659</td>
<td>98.65</td>
<td>326</td>
<td>97.02</td>
<td>1.63%</td>
</tr>
<tr>
<td></td>
<td>Uncorrected</td>
<td>504</td>
<td>75.45</td>
<td>223</td>
<td>66.37</td>
<td>9.08%</td>
</tr>
</tbody>
</table>

CI: Confidence Interval

In the m-ITT, the PCR-corrected cure rates at day 63 were 96.97% for DHA/PPQ group vs. 95.29% for the AS+MQ group (p = 0.161). The lower limit of the 97.5% one-sided CI of the difference (DHA/PPQ-AS+MQ) was -0.84%. In the PP population, the PCR-corrected cure rates at day 63 were 98.65% for the DHA/PPQ group vs. 97.02% for the AS+MQ group (p = 0.074). The lower limit of the 97.5% one-sided CI was -0.39%. Both the two mentioned CIs have lower limits above the non-inferiority margin of -5%, demonstrating that DHA/PPQ is non-inferior to AS+MQ. This finding was confirmed by the results on the pure ITT population and the results of all sensitivity analyses. The performance of AS+MQ was comparable with the expectations from previous studies, therefore the trial was proved to have good assay sensitivity.

The estimate of the true failure rate, defined in accordance with the WHO criteria, was less than 5% (the currently "revised" WHO threshold) for both treatment groups at all considered time-points (Days 28, 42, and 63) and in any case always in favour of DHA/PPQ group. When dividing these treatment failures between early (ETF) and late (LTF), at Day 63, there were no statistically significant differences between treatments, in either of the considered populations. On the contrary, at Days 28 and 42, there was a statistically significant difference between treatments in the proportion of patients with LTF in all efficacy populations. These differences were in favour of DHA/PPQ.

The difference between uncorrected cure rates at day 63 in the DHA/PPQ group compared to AS+MQ was statistically significant in the two co-primary populations. In the m-ITT population, the rates were 71.07% for the DHA/PPQ group vs. 62.88% for AS+MQ (p=0.006). In the PP population, the rates were 75.45% for DHA/PPQ vs. 66.37% for AS+MQ (p=0.002). The lower limit of the CI of...
the difference (DHA/PPQ - AS+MQ) was 2.22% in the m-ITT and 3.07% in the PP populations. The results in the pure ITT population were similar.

There was no statistically significant difference between treatment groups in the proportion of both aperasitaemic patients and afebrile patients up to Day 3 in either the m-ITT or PP populations (at Day 3, the proportions of aperasitaemic patients (DHA/PPQ vs AS+MQ) were 69.97% vs 71.19% in the m-ITT population and 69.46% vs 70.83% in the PP population). The median time to parasite clearance (Kaplan-Meier estimate) was 2 days for both DHA/PPQ and AS+MQ, in all three study populations.

In the m-ITT and PP populations there was a statistically significant difference (up to Day 28 and 21, respectively), between treatments in the proportion of patients with gametocytes. Overall, gametocyte prevalence in the DHA/PPQ group was twice the one in the AS+MQ group: 9.69% vs. 4.80%, respectively (m-ITT population). Similar results were seen in the PP population. These data indicate that DHA/PPQ has less gametocytocidal effect than AS+MQ. However, an ad-hoc study, in which the viability of the gametocytes is tested, would be needed to verify whether the gametocytes surviving the DHA/PPQ treatment are still infectious. Anyway, ACTs are known to reduce gametocyte carriage markedly, and thus to reduce transmission, so even though DHA/PPQ is apparently less gametocyodal than AS+MQ, it is still likely to be better than other anti-malarial drug classes.

**Phase III African Study**

This study enrolled both male and female paediatric patients, aged between 6 and 59 months inclusive, with a body weight of at least 5 kg and who had microscopically confirmed *P. falciparum* malaria and a history of fever (auxiliary temperature at ≥ 37.5°C).

A total of 1553 patients were randomised in the trial with an allocation ratio of 2:1 (DHA/PPQ : A/L). The dosing regimen was calculated by body weight as shown above. A/L (Coartem™) was used in accordance with its Summary of Product characteristics (Novartis, 2007).

The primary and secondary efficacy endpoints were the same as the Asian study with the exception of timing: the primary time-point was Day 28 while the secondary time-points were Days 14 and 42. Efficacy analyses were performed on the pure ITT, m-ITT, and the PP populations, that were defined as in the previously described study.

Demographic characteristics of the study population are summarized in the table below.
### Summary of demographic characteristics in the Phase III African study

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>DHA/PPQ</th>
<th>A/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety/Pure-ITT</td>
<td>m-ITT</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>1038</td>
<td>1027</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>525 (50.58%)</td>
<td>517 (50.34%)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>513 (49.2%)</td>
<td>510 (49.66%)</td>
</tr>
<tr>
<td><strong>Mean Age (Years)</strong></td>
<td>2.42</td>
<td>2.42</td>
</tr>
<tr>
<td><strong>Median Age (Years)</strong></td>
<td>2.28</td>
<td>2.28</td>
</tr>
<tr>
<td><strong>Age Range (Years)</strong></td>
<td>0.51-6.99</td>
<td>0.51-6.99</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>1036 (99.81%)</td>
<td>1025 (99.81%)</td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>1 (0.10%)</td>
<td>1 (0.10%)</td>
</tr>
<tr>
<td><strong>Other Race</strong></td>
<td>1 (0.10%)</td>
<td>1 (0.10%)</td>
</tr>
<tr>
<td><strong>Mean Weight (kg)</strong></td>
<td>11.19</td>
<td>11.19</td>
</tr>
<tr>
<td><strong>Median Weight (kg)</strong></td>
<td>11.00</td>
<td>11.00</td>
</tr>
<tr>
<td><strong>Weight Range (kg)</strong></td>
<td>6.07-25.50</td>
<td>6.07-25.50</td>
</tr>
</tbody>
</table>
The PCR-corrected and uncorrected cure rates at Day 28 are summarised in the table below.

### PCR-corrected and uncorrected cure rates at Day 28 in the Phase III African study

<table>
<thead>
<tr>
<th>Study Population (n)*</th>
<th>Cure Rate</th>
<th>DHA/PPQ</th>
<th>A/L</th>
<th>Treatment Difference (DHA/PPQ – A/L)</th>
<th>Lower Limit of one-sided 97.5% CI</th>
<th>Chi-square test, p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Without Continuity Correction</td>
<td>With Continuity Correction</td>
</tr>
<tr>
<td>Pure-ITT (n=1038, 510)</td>
<td>PCR-corrected</td>
<td>938</td>
<td>90.37</td>
<td>459</td>
<td>90.00</td>
<td>0.37%</td>
</tr>
<tr>
<td></td>
<td>Uncorrected</td>
<td>910</td>
<td>87.67</td>
<td>391</td>
<td>76.67</td>
<td>11.0%</td>
</tr>
<tr>
<td>m-ITT (n=1027,497)</td>
<td>PCR-corrected</td>
<td>952</td>
<td>92.70</td>
<td>471</td>
<td>94.77</td>
<td>-2.07%</td>
</tr>
<tr>
<td></td>
<td>Uncorrected</td>
<td>910</td>
<td>88.61</td>
<td>391</td>
<td>78.67</td>
<td>9.94%</td>
</tr>
<tr>
<td>PP (n=951,462)</td>
<td>PCR-corrected</td>
<td>910</td>
<td>95.69</td>
<td>442</td>
<td>95.67</td>
<td>0.02%</td>
</tr>
<tr>
<td></td>
<td>Uncorrected</td>
<td>884</td>
<td>92.95</td>
<td>376</td>
<td>81.39</td>
<td>11.56%</td>
</tr>
</tbody>
</table>

* (n= DHA/PPQ, A/L)

In the m-ITT population, the PCR-corrected cure rates at Day 28 were 92.70% for DHA/PPQ and 94.77% for A/L (p = 0.128). The lower limit of the 97.5% one-sided CI of the difference (DHA/PPQ-A/L) was -4.59%. In the PP population, these rates were 95.69% and 95.67% for DHA/PPQ and A/L, respectively (p = 0.988). The lower limit of the 97.5% one-sided CI of the difference (DHA/PPQ-A/L) was -2.24%. The CIs for the two co-primary populations have lower limits above the non-inferiority margin of -5% and therefore demonstrate that DHA/PPQ was non-inferior to A/L. This finding is confirmed by the results on the pure ITT population and the results of all sensitivity analyses. Furthermore, the behaviour of the comparator is as expected from literature and this allows the conclusion that the study is valid.

As for the estimate of the true failure rate, defined in accordance with the WHO criteria, it was less than 5% for both treatment groups, at Day 28. Therefore, the conclusions are the same of the Asian trial, i.e. the efficacy definition of WHO is met. The overall treatment failure was 8.76% for DHA/PPQ and 18.71% for A/L, in the m-ITT, and 5.99% vs. 17.10%, respectively, in the PP population. This treatment unbalance is explained by the difference in LTF rates between treatments, which was in favor of DHA/PPQ. However, there were more ETFs in the DHA/PPQ group compared with the A/L group (1.17% vs. 0.40%, respectively, in the m-ITT). The most frequent reason for ETF was persistent vomiting at Day 0 with the use of quinine or i.v. artesunate at Day 0 (n = 9 vs. n = 2, for DHA/PPQ and A/L, respectively).
Further analysis of the data showed that the uncorrected cure rate at Day 28 was substantially higher for DHA/PPQ compared with A/L. In the m-ITT population, the uncorrected cure rate at Day 28 was 88.61% for DHA/PPQ vs. 78.67% for A/L, with a treatment difference of 9.94% (p < 0.001). In the PP population, the same estimate was 92.95% for DHA/PPQ vs. 81.39% for A/L, with a treatment difference of 11.56% (p < 0.001). These results are confirmed in the pure ITT population.

Since the rate of recrudescences is comparable between the two treatment groups, the treatment difference observed in the uncorrected cure rate was mainly due to fewer new infections with DHA/PPQ as compared to A/L. These data indicate that DHA/PPQ confers more protection from acquiring new \( P. falciparum \) infections than A/L. This added protection is a tremendous advantage in Africa where malaria is hyper-endemic with an associated high morbidity, especially in young children.

In the m-ITT, 36.03% of DHA/PPQ treated patients were aparasitaemic on Day 1 (24h after starting treatment) compared with 28.57% of A/L-treated patients. This difference between treatments was statistically significant (Chi-square test, p = 0.003). By Day 3, 97.66% and 98.39% of DHA/PPQ and A/L-treated patients respectively were aparasitaemic (Chi-square test, p = 0.279). Very similar patterns were observed in the ITT and PP populations. The median time to parasite clearance (Kaplan-Meier estimate) was 2 days for both DHA/PPQ and A/L, in all three study populations.

No difference was observed between the two compared treatment groups on the results for overall fever clearance.

The proportion of patients with gametocytes at enrolment was similar between treatment groups (m-ITT population: 11.78% in DHA/PPQ vs. 13.28% in A/L, p = 0.403; PP population: 11.36% in DHA/PPQ vs. 12.99% in A/L, p = 0.374). However, by Day 2, it was noted that the percentage of patients with gametocytæmia was greater in the DHA/PPQ group compared with the A/L group: 16.65% vs. 9.26% respectively, in the m-ITT population and 16.09% vs. 9.09% respectively, in the PP population (Chi-square test, p < 0.001). This difference persisted and was statistically significant until Day 21 in both study populations. These data confirm that DHA/PPQ could have less gametocydal effect than A/L.

**Phasel/II Studies**

Efficacy data have been also collected in two pharmacokinetics trials carried out in patients with uncomplicated \( P. falciparum \) malaria.

One trial (Study ST3073+ST3074 DM04008) was carried out in Burkina Faso, where 32 children (≥1 year, ≤5 years) have been treated with DHA/PPQ. The Day 28 PRC-corrected cure rate was 87.5% in the ITT population and 93.3% in the PP population.

The other trial (Study ST3073+ST3074 DM04009) was carried out in Thailand where 25 adult patients with uncomplicated \( P. falciparum \) malaria have been treated with DHA/PPQ. The Day 90 PCR-corrected cure rate was 100% in the ITT population.

**Efficacy Findings from Other Clinical Trials Reported in the Literature**

Additional efficacy data are available from studies conducted between 2005 and 2008 (in 2005 the study by Ashely et al. 2005 changed the dosing regimen of DHA/PPQ from four to three}
doses). These studies were identified by a combined MEDLINE and EMBASE search, and were selected for their similarity to the design and comparators of the sigma-tau studies. These studies were mostly performed as investigator-initiated studies, and showed efficacy results very similar to the sigma-tau studies.

**Summary of Comparative Efficacy against Comparators**

Similar results as those observed in the Asian and African Phase III have been reported in the literature.

In a review (Myint HY *et al.* 2007) fourteen clinical trials on combinations containing DHA/PPQ have been analysed. These studies were published in 13 articles between 2002 and October 2006. There was a total of 2,636 patients (22 treatment arms) exposed to DHA/PPQ for the treatment of multidrug-resistant uncomplicated *P. falciparum* malaria. The efficacy in these studies of DHA/PPQ in multidrug-resistant falciparum malaria was excellent, with overall 28-day cure rates or Kaplan-Meier derived estimates of ~97-98% in China, Cambodia, Myanmar, Laos PDR, Thailand and Vietnam. In the comparative studies the efficacy of DHA/PPQ was as good as MQ/AS and it was better than artesunate + amodiaquine.

From 2007 till 2010 several other publications (Grande T, 2007; Hasugian AR, 2007; Jannsens B, 2007; Kamya MR, 2007; Zongo I, 2007; Karunajeewa HA, 2008; Yeka A, 2008; Arinaitwe E, 2009; Thanh XN, 2009; Adam I, 2010; Smithuis F, 2010) reported similar results, i.e. the PCR-corrected cure rate observed with DHA/PPQ was at least not inferior to the other ACTs used as comparators (AS/MQ, A/L and AS/AQ), while the uncorrected cure rate was always in favour of DHA/PPQ, indicating a lower incidence of new infections during the follow up (day 42 and/or day 63).

The most recent large clinical trial reported with DHA/PPQ has been presented at the 59th congress of the American Society of Tropical Medicine & Hygiene (D’Alessandro U *et al.*, 2010). A total of 4,116 patients, African children <5 years with uncomplicated *P. falciparum* malaria, was treated with four ACTs: 1,226 with A/L, 1,002 with AS/AQ, 413 with CDA and 1,475 with DHA/PPQ. The Investigational Sites were 10 in 7 African Countries (Burkina Faso, Nigeria, Gabon, Zambia, Uganda, Rwanda and Mozambique). The PCR-corrected cure rate at day 63 showed no differences between DHA/PPQ, A/L and AS/AQ, while these three ACTs were statistically superior in comparison with CDA. The PCR-uncorrected cure rate at day 63 indicated that DHA/PPQ was statistically superior to A/L, AS/AQ and CDA.

**Conclusions on Efficacy of Eurartesim in P. falciparum Uncomplicated Malaria**

In clinical trials sponsored by Sigma-Tau and in all spontaneous studies carried-out in several countries, DHA/PPQ has been shown to be similar in terms of PCR-corrected cure rate vs. the comparators in treating uncomplicated *P. falciparum* malaria. It has also been shown to confer additional protection following treatment against re-infection (very likely due to the long half-life of PPQ). A summary of comparative effectiveness for DHA/PPQ is presented at the end of section 11.
Efficacy of Eurartesim in *P. vivax* Uncomplicated Malaria

Several published trials investigated the efficacy or effectiveness of ACTs for the treatment of the uncomplicated *P. vivax* malaria in chloroquine-resistant areas. The most commonly investigated combinations have been DHA/PPQ, A/L, AS/AQ and AS+SP. Among them, the DHA/PPQ combination appeared to be the most promising therapy in terms of efficacy, safety and prophylactic effect against relapses.

The second edition of the WHO Guidelines for the treatment of malaria indicate that “in areas with chloroquine resistant *P. vivax*, artemisinin-based combination therapies (particularly with those whose partner medicines have long-half lives) are recommended for the treatment of *P. vivax* malaria.” and in particular that “In areas where infections of drug-resistant *P. falciparum* and/or *P. vivax* are common, drug regimens to treat both species effectively must be used. An artemisinin-based combination treatment (particularly dihydroartemisinin plus piperaquine) that does not include sulfadoxine-pyrimethamine would be a good choice.”

The recommendation is based on the results from the following studies: two trials (Hasugian AR, et al, 2007; Ratcliff A et al., 2007) compared DHA/PPQ to alternative ACTs (A/L and AS+AQ) in Indonesia where all groups were also given primaquine to clear the liver stage parasites. DHA/PPQ reduced the number of relapses by day 42 compared to AL (1 trial, 126 participants; RR 0.16, 95% CI 0.07–0.38; moderate quality evidence) and AS+AQ (1 trial, 84 participants; RR 0.16, 95% CI 0.05–0.49; moderate quality evidence). There are no trials comparing DHA/PPQ and AS+MQ in *P. vivax* mono-infection. At day 42, the patients in the DHA/PPQ groups were also less likely to be anaemic, although this data includes participants with *P. falciparum* mono-infection at baseline, and recurrence of *P. falciparum* was also lower with DHA/PPQ. This effect is likely to be a prophylactic effect related to the longer half-life of DHA/PPQ.
11. Summary of Comparative Evidence on Safety

Patient Exposure

The safety database for exposure to DHA/PPQ consists primarily of data from eight clinical studies sponsored by sigma tau in 1862 adult and paediatric patients with malaria, and in 392 healthy volunteers. In each case, all randomised patients who received at least one dose of study medication were included in the safety analyses (see table below).

<table>
<thead>
<tr>
<th>Study number</th>
<th>Study population</th>
<th>n (total)</th>
<th>n (Eurartesim)</th>
<th>n (comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single dose exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST CRO-PK-05-138 (ART-DFM-05-002)</td>
<td>Adult healthy volunteers. Caucasian race. Study performed in Switzerland.</td>
<td>16</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Study DM-09-008 (Food effect)</td>
<td>Male adult healthy volunteers. Caucasian race. Study performed in Australia.</td>
<td>36</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td><strong>Full 3-day treatment course</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study DM-09-006 (QT/QTc study)</td>
<td>Healthy male/female volunteers. Caucasian race. Study performed in France.</td>
<td>268</td>
<td>184</td>
<td>84</td>
</tr>
<tr>
<td>Study DM-09-007 (PK study)</td>
<td>Healthy male/female volunteers. Asian and Caucasian race. Study performed in Australia.</td>
<td>72</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td>Study DM-04-009</td>
<td>Adult malaria patients. Asian race. Study performed in Asia.</td>
<td>25</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Study DM-04-008</td>
<td>Paediatric malaria patients (aged 1-5 yrs). Black race. Study performed in Africa.</td>
<td>32</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>Study DM040010 (Pivotal)</td>
<td>Malaria patients (aged 8 months - 62 yrs). Asian race. Study performed in Asia.</td>
<td>1,148</td>
<td>767</td>
<td>381</td>
</tr>
<tr>
<td>Study DM040011 (Pivotal)</td>
<td>Paediatric malaria patients (aged 6 to 59 months). Black race. Study performed in Africa.</td>
<td>1,548</td>
<td>1,038</td>
<td>510</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>3,145</td>
<td>2,170</td>
<td>975</td>
</tr>
</tbody>
</table>

The number of adult and paediatric patients in the above database is as follows:
• 1,239 patients were aged <18 years;
• 566 patients were aged ≥18 years.

Given the very limited numerical contribution of the pediatric patient population from the Asian pivotal study, as well as of the respective Phase I/II studies to the patient populations enrolled in the pivotal studies, it was not deemed appropriate to integrate the safety data of patients in all studies.

All exposed patients received DHA and PPQ in the same 1:8 ratio, adjusted by body weight according to the table presented in section 9. In addition, safety data are available from two spontaneous studies using Eurartesim (provided by Sigma-tau) in 4,590 patients enrolled up to May 30, 2009, as well as from 26 studies identified from an interrogation of the literature databases and conducted between 2002 and 2008 on over 7,900 malaria patients, exposed to DHA/PPQ and other anti-malarials.

In these trials, the doses administered were also adjusted according to body weight. The adult doses of DHA and PPQ used in these studies (mimicking those proposed for Eurartesim) are similar to those used historically when the two drugs were given as monotherapy (Davis et al, 2005).

**Description of Adverse Effects/Reactions**

**Clinical pharmacology studies sponsored by Sigma-tau**

The safety profile in Study ART-DFM-05-002 appeared very benign, since subjects received only one dose of Eurartesim to account for a lower drug exposure than a malaria patient (due to the absence of "disease effect" on drug disposition).

All the observed events in Studies DM 04008 and DM 04009 were consistent with acute malaria infection. Specifically:
- There were no deaths, or withdrawals due to AEs;
- There was one serious AE (convulsion on Day 0), almost certainly a consequence of malarial infection, which resolved successfully;
- Recurrent malaria accounted for most reported events (e.g. cough, pneumonia, diarrhoea, anaemia);
- All events were of mild intensity;
- Only one event (P. falciparum malaria) was classified as possibly related to study drug, although a true causal relationship seems highly unlikely.
- Laboratory abnormalities were common and consistent with acute malaria.

In conclusion, there was no evidence of an emerging drug-related safety signal.

**Pivotal studies sponsored by Sigma-tau**

There were 2 deaths in the pivotal study programme (both occurring in Study DM04011: one in DHA/PPQ and one in A/L). No concerns arise from the incidence of such a number of deaths in the respective treatment groups, or from a detailed consideration of the individual narratives.

The incidence of the serious treatment-emergent adverse events (TEAEs), plus the serious TEAEs related to the study drug, in the pivotal studies is summarised in the table below:
Serious Treatment-Emergent Adverse Events in Pivotal Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Total STEAEs</th>
<th>Total STEAEs (DHA/PPQ)</th>
<th>Related STEAEs (DHA/PPQ)</th>
<th>Total STEAEs (Comparator)</th>
<th>Related STEAEs (Comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM040010</td>
<td>15 (1.3%)</td>
<td>12 (1.6%)</td>
<td>6 (0.8%)</td>
<td>3 (0.8%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>(Asia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM040011</td>
<td>23 (1.5%)</td>
<td>18 (1.7%)</td>
<td>15 (1.5%)</td>
<td>5 (1.0%)</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>(Africa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There were no statistically significant differences in the number of serious TEAEs or drug-related serious TEAEs between treatment groups, in either study. Two serious TEAEs of “anaemia” in the Eurartesim group of Study DM04010 are in fact likely to have been due to disease pathology rather than to drug treatment. In addition, one case of Wolf-Parkinson-White syndrome was recorded as a serious TEAE: since this is in fact a congenital condition, this assignment of relatedness appears incorrect.

Overall, the nature of serious TEAEs is in line with expectations for this patient population. The distribution of serious TEAEs between treatment groups gives no cause for concern.

The most common adverse events in the pivotal studies are shown in the table below:

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Proportion of patients (%)</th>
<th>Study DM04010 (Asia)</th>
<th>Study DM04011 (Africa)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DHA/PPQ</td>
<td>AS+MQ</td>
</tr>
<tr>
<td>Headache</td>
<td>18.0</td>
<td>20.2</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>14.5</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td><em>P. falciparum</em> Infection</td>
<td>13.4</td>
<td>15.2</td>
<td>19.0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10.6</td>
<td>11.3</td>
<td>29.1</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>8.5</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>7.8</td>
<td>9.7</td>
<td>39.8</td>
</tr>
<tr>
<td>Anaemia</td>
<td>7.2</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>6.0</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5.5</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>ECG QT corrected prolonged</td>
<td>5.4</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5.2</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>5.0</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>5.0</td>
<td>5.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.9</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5</td>
<td>6.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.4</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td>21.0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td>13.7</td>
</tr>
</tbody>
</table>

AS+MQ: artesunate+mefloquine; A/L: arthemether/lumefantrine (Coartem)
Five common events were recorded in both pivotal studies. The most notable finding is the incidence of *P. falciparum* infection. The between-group differences were 1.8% and 6.9% (both in favour of Eurartesim). The apparent reduced rate of new falciparum infection following treatment with Eurartesim is certainly of relevance to any patient who remains in a malaria endemic area. The larger treatment difference observed in the African study probably reflects the fact that this is an area of stable transmission (and therefore the risk of new infection is inherently higher). Pyrexia, anorexia and vomiting occurred with similar or lower frequency in the Eurartesim groups than in the comparator groups. Incidence of cough was lower for Eurartesim in the Asian study and higher in the African study, but in each case the difference was no more than 2%.

Adverse events occurring at any frequency and for which a between-group frequency difference of ≥2% was observed are shown in the table below:

**TEAEs with Between-group Differences ≥2% in Pivotal Studies**

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Study DM04010 (Asia)</th>
<th>Study DM04011 (Africa)</th>
<th>Δ (%) *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DHA/PPQ</td>
<td>AS+MQ</td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>4.2</td>
<td>1.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.9</td>
<td>6.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5</td>
<td>6.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5.0</td>
<td>7.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Malaria</td>
<td>14.5</td>
<td>22.6</td>
<td>8.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.4</td>
<td>6.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Headache</td>
<td>18.0</td>
<td>20.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. falciparum</em> infection</td>
<td>19.0</td>
<td>25.9</td>
<td>6.9</td>
</tr>
</tbody>
</table>

AS+MQ: artesunate+mefloquine; A/L: arthemether/lumefantrine (Coartem)

* Values on the left of the column indicate an excess in the DHA/PPQ group; numbers on the right of the column indicate an excess in the comparator group.

The key observations are:

- Only 2 events in the pivotal studies (sinus bradycardia and influenza) registered an excess of ≥2% in the DHA/PPQ group.
- Far more events (8 events) were more frequent in the comparator arms. These included malaria (8.1% excess in the Asian study) and *P. falciparum* infection (6.9% excess in the African study).

Assessments of relatedness concluded that nausea, asthenia, dizziness, influenza, *P. falciparum* infection and anorexia were the only TEAEs related to treatment. Of these, only influenza occurred more frequently in the DHA/PPQ groups. The remaining drug-related TEAEs were all less common on DHA/PPQ than on comparator.
The overall picture with regard to the incidence of TEAEs is therefore highly reassuring. Very few events were recorded at higher frequency for DHA/PPQ than in comparator groups; even here, the excesses were modest and the events themselves are not of major clinical concern. In general, excesses in the comparator groups were also modest, with the important exceptions of new malaria infections. These occurred with very considerably higher frequency in comparator arms, strongly implying an advantage of real clinical importance for DHA/PPQ.

In addition to adverse events, the following parameters were examined in the pivotal studies sponsored by Sigma-tau:

1. **Physical examinations and vital signs:** Changes in vital signs from baseline to end-of-study were all directly attributable to recovery from malaria and were apparent irrespective of treatment allocation.

2. **Laboratory values:** Haematology and biochemistry evaluations (both pivotal studies) plus urinalysis results (Study DM04010 only) showed changes from baseline to end-of-study. These changes were all directly attributable to recovery from malaria and were apparent irrespective of treatment allocation. There was no evidence of any unwanted effect of DHA / PPQ treatment on any laboratory parameter.

3. **ECGs:** A rigorous evaluation of cardiac safety was undertaken in the pivotal studies. ECGs were taken on Days 0, 2 and 7 and centrally read; the QTc prolongation potential was analysed according to the ICH E14 guideline. The analyses showed that:
   - At baseline, a QTc prolongation is associated with the malaria infection state;
   - On Day 2, a higher proportions of patients with borderline and prolonged QTc values were present in the DHA/PPQ group with comparison to the comparator groups;
   - By Day 7, differences in the proportions of patients with borderline and prolonged QTc had resolved;
   - No patients with QTc >500msec were present in either study at any timepoint.
   - This short-term QTc prolongation does not translate into a tangible risk of suffering clinically significant TEAEs that are known to be associated with QT interval prolongation.

To clarify the relevance of the above ECG findings, Sigma-tau agreed with EMA’s request to perform a thorough QTc study. The study enrolled healthy volunteers being administered DHA/PPQ either in fasting conditions (n=40), or following a low (n=64) or high (n=40) Kcal meal. Control subjects were administered A/L after a low Kcal meal (n=64 subjects), or placebo plus moxifloxacin (n=40 subjects).

The results of this study showed that there was a food-dependent effect of Eurartesim™ on the QTc prolongation, which correlates with the plasma levels of PPQ, while it is quite independent of DHA plasma concentrations. Specifically:

- In fasting condition, DHA/PPQ causes a mean QTcF prolongation of 21.0 ms (95% CI: 15.7-26.4 ms) over placebo. This change is similar to that reported in patients (Mytton OT, 2007), where the prolongation for QTcF was 29 ms. If we consider about 10 ms the QTcF prolongation given by placebo (not used in this trial), the “true value” should be around +20 ms. The Authors concluded that “at therapeutic doses, DP does not have clinically significant effects on the electrocardiogram.”
- No subject in the DHA/PPQ fasting arm had a maximum time-matched actual value of QTcF greater than 480 ms, nor a maximum time-matched change from baseline greater than 60 msec, both being thresholds of concern.
Due to these findings, DHA/PPQ dosing conditions have been modified in the Summary of Product Characteristics (SmPC), which now states that Eurartesim should be administered with water without food.

**Safety of DHA/PPQ in Published Studies**

DHA/PPQ in a 1:8 ratio is commercially available in Africa (as DuoCotecxin™) and Asia (as Artekin™). Data on the safety of these products is available from the published literature. Twenty-six studies were identified following an interrogation of both MEDLINE and EMBASE databases, which were conducted between 2002 and 2008, on over 7,900 malaria patients exposed to DHA/PPQ and other anti-malarials.

Review of these studies showed that DHA/PPQ is overall well tolerated, having a low incidence of TEAEs and a mild severity. In comparing the literature studies from each endemic area to the Sigma tau studies in the same areas and age categories, it can be seen that a comparable AE profile is observed, with the TEAEs reported in the sigma tau studies being similar to those reported in the literature, and very often being confounded by the underlying disease.

**Safety of DHA/PPQ in Spontaneous Studies**

DHA/PPQ manufactured by Sigma tau has been used in 2 spontaneous clinical trials (Principal Investigators: U. D’Alessandro and S. Bormann), which have enrolled a total of 4,590 patients so far. The safety profile of DHA/PPQ shown so far in these studies is similar to that observed in the Sigma tau studies.

**Variation in Safety due to Patient Factors**

The possible impact of intrinsic factors (age, gender, body mass index, parasite density at baseline and liver abnormalities) or of extrinsic factors (dose/kg of treatment received and use of selected concomitant medication) on the safety profile of DHA/PPQ was assessed: no clinically significant effects were found. The occasional statistically significant results obtained can be regarded as random and most probably unrelated to DHA/PPQ administration.

QTc prolongation was the most variable and sensitive parameter but, as already discussed, it was asymptomatic. Interestingly, DHA/PPQ treatment did not worsen the AE profile in patients with ECG abnormalities at baseline, irrespective of age, gender and parasite density at baseline; in addition, there did not appear to be a correlation between the total dose/kg of treatment received and QTc interval.

Pregnancy was an exclusion criterion in Study DM04010 and therefore there is no direct experience with DHA/PPQ in pregnancy. The warnings on use in pregnancy present in the SmPC are in line with the WHO guidance on the use of artemisinins in pregnancy and are therefore considered appropriate.
Summary of Comparative Safety against Comparators

See above for a discussion of the safety profile of DHA/PPQ, when compared to other drugs in pivotal studies (A/L and AS+MQ).

Conclusions on Safety

The number of patients treated with DHA/PPQ in the Sigma-tau clinical programme is large for a combination about which so much safety data has already been published (n>1,850); it is also comprehensive with respect to age range. The observed safety profile is in line with expectations from published literature.

In the pivotal studies, DHA/PPQ was generally associated with fewer TEAEs than comparators in most system organ classes, with the exception of the cardiovascular system, where a small excess of TEAEs was seen in the DHA/PPQ group. The most noticeable safety signal relates to the potential for QTc prolongation, which occurred with slightly higher frequency and somewhat greater intensity than it did for comparators. However, these changes were largely asymptomatic – there was no increased rate of AEs associated with QTc prolongation, and occurred in a PPQ and food-dependent fashion. The SmPC provides prescribers with more than adequate warnings and advice relating to this potential risk, which is largely offset by PPQ’s benefit of preventing resistance to artemisinins, and of providing a secondary prophylaxis to new *P. falciparum* infections.

In conclusion, Eurartesim is well tolerated at the tested doses and regimens.

Comparative Effectiveness and Overall Conclusions

Currently there are only two other ACT’s registered on the European market:
- Arthemeter/Lumefantrine (Coartem™/Riamet™, Novartis) available as a co-formulation
- Artesunate + Mefloquine (Mefla™) available as separate tablets

Eurartesim™ proved to be as effective as Coartem™ and Artesunate + Mefloquine. In fact, for all these drugs the therapeutic success in the treatment of uncomplicated *P. falciparum* malaria exceeded the threshold of 95%.

The expected advantages of Eurartesim™ compared to Coartem™ are:
- Favourable compliance: body weight being equal, a patient weighing 60kg must take 24 Coartem™ tablets in 48h vs. 6 of Eurartesim™.
- Lower incidence of re-infections (a very important advantage in endemic areas).
- In addition, Eurartesim™ should be administered with water without food, while Coartem™ requires co-administration with a fatty meal or milk.

With regard to the combination of Artesunate and Mefloquine, the expected advantages of Eurartesim™ are:
- Favourable compliance: the latter is a fixed-dose combination while Artesunate and Mefloquine are co-packaged tablets.
- Better safety profile (see below for QTc prolongation). Artesunate and Mefloquine may cause a greater number of adverse events. Mefloquine causes psychiatric reactions such as depression, mood changes, anxiety, confusion, hallucinations, panic attacks, restlessness, forgetfulness, psychosis, paranoia, emotional instability, aggression, and agitation.
Eurartesim™ causes a longer QTc prolongation as compared with the two above described drugs. However, the intensity and frequency of the QTc prolongation associated with Eurartesim™, when administered with water without food, appears modest (in terms of mean increases from baseline) and transient (completely resolves by day 7).

Eurartesim™ also had less gametocytocidal effect than the two comparators. However, an ad-hoc study would be needed to verify whether the gametocytes surviving the DHA/PPQ treatment are still infectious.

Overall, Eurartesim offers an effective solution to uncomplicated *P. falciparum* malaria when compared to the other existing options.
12. Summary of Available Data on Comparative Cost and Cost Effectiveness Within the Pharmacological Class or Therapeutic Group

As of today, most commercially available DHA/PPQ (not prequalified by WHO, and not approved by stringent regulatory authorities) is available either by gift (typically government-to-government donations) or through private sector sellers who command a significant premium in private pharmacy sales (e.g. DuoCotecxin, Holley-Cotec Pharmaceuticals, may cost $5.00-$8.00 USD or more in private pharmacies in East Africa.) Thus, a comparative cost and cost effectiveness basis for this product based on international open tender procurement for use in the public sector has yet to be established.

After EMA approval is conferred to Eurartesim™ and DHA/PPQ is WHO pre-qualified, Sigma-tau will register it for use in the Affordable Medicine Facility-malaria (AMF-m), as well as for public sector tenders financed, for example, by the Global Fund. Participation in the AMF-m will result in price negotiations designed to ensure affordability for customers in the non-premium private sector, as well as price comparability for public sector procurement of ACTs.

Sigma-tau has committed to making DHA/PPQ accessible and affordable for public sector use, with a target price of USD $1.00/treatment. This should place the product in line with currently available ACTs (artemether-lumefantrine is available at a weighted cost of approximately USD $0.75; for ASAQ Winthrop, the average cost of a full treatment is approximately USD $0.54.)

Lastly, clinical trial Phase III evidence has demonstrated that DHA/PPQ provides the best protection against reinfection, compared to other qualified FDC ACTs. In a recent trial, the proportion of new infections up to Day 42 was 13.55% (95% CI: 11.35%–15.76%) for DHA/PPQ vs 24.00% (95% CI: 20.11%–27.88%) for A/L (p<0.0001). This sizeable difference in diminishing reinfections by nearly 50% compared to A/L will yield significant cost effectiveness benefits when the product establishes an official public sector price and can be used in head-to-head post-launch effectiveness studies.

Eurartesim™ was awarded Orphan Status in Europe (EU/3/07/468) on August 2007 based on the criterion of significant benefit; it has been granted the same status also in the United States on January 2007.

The Applicant has obtained an approval for a Pediatric Investigation Plan (EMEA/PDCO/23353/2009 P/67/2009) by EMA, and has submitted a Marketing Authorization Application to EMA on July 2009. Currently, the review of Eurartesim has progressed and is at the Day-180 timepoint. Approval by EMA is expected in Q1-2, 2011.

Eurartesim™ is not registered anywhere in the world.

DHA/PPQ in a 1:8 ratio is commercially available in Africa (as DuoCotecxin™) and Asia (as Artekin™), manufactured by Holley-Cotec Pharmaceuticals.

Sigma-tau started in 2010 a collaboration with the International Pharmacopeia and the United States Pharmacopoeia on DHA/PPQ. The target is to define an international standard of DHA/PPQ based on the most recent findings by Sigma-tau mainly in the area of stability related impurities both in Drug substances and Drug product. In particular, the International Pharmacopoeia should be upgraded with a new monograph for PPQ drug substance and with a new monograph for the drug product DHA/PPQ, reporting methods able to detect the principal DHA degradation products and to assess the shelf life of the drug combination.
15. Proposed (new/adapted) Text for the WHO Model Formulary

<table>
<thead>
<tr>
<th>6.5.3 Antimalarial medicines</th>
<th>6.5.3.1 For curative treatment</th>
</tr>
</thead>
</table>
| dihydroartemisinin + piperaquine | Tablets:  
40 mg DHA + 320 mg PPQ  
20 mg DHA + 160 mg PPQ  
Not recommended in the first trimester of pregnancy or in children below 5 kg |
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Attachment 1

Letter of Support by Dr. Dennis Schmatz (CEO, Medicine for Malaria Ventures, Switzerland)

Letter of Support by Prof. Nick White (University of Oxford, UK)