



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2011
EMA/739355/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eurartesim

dihydroartemisinin / piperaquine phosphate

Procedure No.: EMEA/H/C/1199

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

| | |
|---|---|
| ACPR | Adequate Clinical and Parasitological Response |
| ACT | Artemisinin-based Combination Therapies |
| AE | Adverse Event |
| AUC | Area under the plasma concentration versus time curve |
| AUC ₀₋₂₄ | Area under the plasma concentration versus time curve, from time 0 to 24h. |
| AUC ₀₋₄₂ | Area Under the plasma Concentration versus time curve from 0 to 42 hrs |
| AUC _{0-last} | Area Under the plasma Concentration versus time curve from 0 to last timepoint |
| AUC _{0-t} | Area Under the plasma Concentration versus time curve from 0 to the last measurable concentration, as calculated by a trapezoidal method. |
| AUC _{0-t} / AUC _{0-∞} | The ratio of AUC _{0-t} to AUC _{0-∞} |
| AUC _{0-∞} | Area Under the plasma Concentration versus time curve from 0 to infinity. AUC _{0-∞} was calculated as the sum of AUC _{0-t} plus the ratio of the last measurable plasma concentration to the elimination rate constant. |
| BLQ | Below the Level of Quantification |
| BMI | Body Mass Index |
| C _b | Concentration in blood |
| C _p | Concentration in plasma |
| CI | Confidence Interval |
| CL | Total Body Clearance |
| CL/F | The apparent total body clearance after extra-vascular administration, calculated as Dose/AUC _{0-∞} |
| CL _d /F | Apparent distributional clearance |
| C _{max} | Maximum measured plasma concentration over the time span specified |
| Conc | Concentration |
| CV | Coefficient of variation of the mean |
| CYP450 | Cytochrome P450 |
| DBP | Diastolic Blood Pressure |
| DHA | Dihydroartemisinin |
| ECG | electrocardiogram |
| F | Bioavailability |
| F _R | Relative Bioavailability |
| GLP | Good Laboratory Practice |
| h | Hour |
| HR | Heart Rate |
| IC(50) | Half Maximal inhibitory concentration |
| LLOQ | Lower limit of quantification |
| LOD | Limit of detection |
| LOQ | Limit of Quantification |
| M | Molar, mol per litre |
| min | Minute |
| mM | Millimolar |
| mmHg | Millimetres of Mercury |
| ms | Millisecond |
| PCR | Polymerase Chain Reaction |
| PK | Pharmacokinetic |
| PQ | Piperaquine (free drug measured in plasma) |
| PQP | Piperaquine phosphate (salt used in dosage form) |
| SAE | Serious Adverse Event |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |

| | |
|--------------|--|
| SOP | Standard Operating Procedure |
| $t_{1/2}$ | Apparent first-order terminal half-life was calculated as 0.693/kel. |
| Tlag | Duration of time before the drug starts to be detected in plasma following oral administration |
| T_{max} | Time of the maximum measured plasma concentration |
| V_{area}/F | The apparent total volume of distribution after extra-vascular administration, calculated as $Dose/(AUC_{0-\infty} * kel)$. |
| V_c/F | Apparent Volume of the Central Compartment |
| V_d | Volume of distribution |
| V_d/F | Volume of distribution relative to bioavailability |
| V_{dss}/F | Volume of distribution at steady state relative to bioavailability |
| V_p/F | Apparent volume of peripheral compartment |
| V_{ss}/F | Total Apparent Volume of Distribution |
| V_z/F | Volume of Distribution associated with the terminal phase |
| WBC | White Blood Cell |

| | |
|----------------------|--|
| % | Percent |
| ▲ | Difference |
| °C | Degree Centigrade |
| ACPR | Adequate Clinical and Parasitological Response |
| ACT | Artemisinin-based Combination Therapy |
| AE | Adverse event |
| AIDS | Acquired Immunodeficiency Syndrome |
| A/L | Artemether-lumefantrine |
| AQ | Amodiaquine |
| AS | Artesunate |
| AS+MQ | Artesunate + mefloquine regimens |
| AUC | Area Under the Curve |
| CI | Confidence Interval |
| c-PCR | PCR-corrected (cure rate) |
| CTD | Common Technical Document |
| DBP | Diastolic blood pressure |
| DHA | Dihydroartemisinin |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| ETF | Early Treatment Failure |
| EU | European Union |
| FU | Follow-up |
| h | Hour |
| Hb | Hemoglobin |
| HIV | Human Immunodeficiency Virus |
| HR | Heart rate |
| ITT | Intention-To-Treat (statistical analysis) |
| Kg | Kilograms |
| LCF | Late Clinical Failure |
| LOCF | Last Observation Carried Forward |
| LPF | Late Parasitological Failure |
| LTF | Late Treatment Failure |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligrams |
| m-ITT | Modified Intention-To-Treat (statistical analysis) |
| MQ | Mefloquine |
| n | Number |
| NS | Not significant |
| od | Once-daily |
| OR | Odds Ratio |
| p | Probability |
| <i>P. falciparum</i> | <i>Plasmodium falciparum</i> |
| <i>P. vivax</i> | <i>Plasmodium vivax</i> |
| PC 50/90 | Time to reduce initial parasite count by 50%/90%, respectively |
| PCR | Polymerase-chain Reaction |
| PCT | Parasite Clearance Time |
| PCV | Packed cell volume |
| PK | Pharmacokinetic |
| po | per os (orally) |
| PP | Per Protocol (statistical analysis) |
| PQP | Piperaquine tetraphosphate |
| QC | Quality Control |
| RBCs | Red Blood Cells |
| RD | Risk Difference |
| RR | Respiratory Rate |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SD | Standard Deviation |
| t _{1/2} | half-life |
| TF | Treatment Failure |

ULN
u-PCR
vs
WBC
WHO

Upper limit of normal
Uncorrected-PCR (cure rate)
Versus
White Blood Cell
World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sigma-tau Industrie Farmaceutiche Riunite S.p.A. submitted on 06 July 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Eurartesim, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 March 2008.

Following the CHMP positive opinion and at the time of the review of the orphan designation by the Committee on Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 14 July 2011 on request of the sponsor.

The applicant applied for the following indication "For the treatment of uncomplicated *Plasmodium falciparum* malaria and for reducing the risk of new infections".

The legal basis for this application refers to

Article 8.3 of Directive 2001/83/EC

The application submitted is:

Composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Derogation from market exclusivity

Not applicable.

Scientific advice

The applicant received Scientific Advice from a Member State (United Kingdom) on 30 December 2007.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Ian Hudson**

Co-Rapporteur: **Martina Weise**

- The application was received by the EMA on 06 July 2009.
- The procedure started on 22 July 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 October 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 October 2009.
- During the meeting on 20 May 2010 and re-adoption on 24 June 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 06 July 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 May 2010 and 09 August 2010.
- The summary report of the inspection carried out at the following sites Zambia, Kenya, and at the sponsor site between 13-16 September 2010, 20-23 September 2010 and 05-09 July 2010 to the conduct of trial DM040011, was issued on 29 October 2010. The final GCP Inspection report was circulated to CHMP on 21 January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 October 2010.
- During the CHMP meeting on 21 October 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 December 2010.
- During a meeting of an Ad-Hoc Expert Group on 14 January 2011, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 14-17 February 2011, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 17 March 2011, the CHMP agreed on a follow-up outstanding issue to be addressed in a further oral explanation by the applicant.
- The applicant submitted responses to the CHMP on 13 June 2011.
- During the CHMP meeting on 20-23 June 2011, remaining outstanding issues with reference to cardiac safety were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20-23 June 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation.

2. Scientific discussion

2.1. Introduction

Problem statement

Malaria remains a major cause of morbidity and death in endemic areas and substantial numbers of travellers 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*. Of the classical 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.

Thus far the only medicinal product approved in the EU that would meet this requirement is a fixed combination of artemether and lumefantrine. Another widely recommended treatment option in non-endemic areas, such as EU, is the fixed combination of atovaquone and proguanil.

Artemisinin and its derivatives

A crude extract of the wormwood plant *Artemisia annua* (qinghao) was first used as an antipyretic 2000 years ago in China and its specific effect on fever associated with malaria was reported in the 16th century. The active constituent of the extract was identified and purified in the 1970s and named qinghaosu or artemisinin.

Although artemisinin proved effective in clinical trials in the 1980s, a number of semi-synthetic derivatives were developed that had improvements in pharmacological properties, including pharmacokinetics and activity against malaria parasites. While the artemisinin derivatives are active per se against Plasmodia they undergo variable conversion to an active metabolite – dihydroartemisinin (DHA) - which preferentially accumulates in *P. falciparum*-infected erythrocytes. The bioavailability of dihydroartemisinin from oral artesunate has been estimated to be about 80%, whereas the bioavailability of artesunate itself is only 15%.

The artemisinins are highly active against asexual forms of the four species of *Plasmodium* that infect humans with very rapid reductions in parasitaemia but relatively short plasma half-lives. There is also activity against the sexual forms (gametocytes) and therefore these agents have some potential to reduce transmission rates.

While the exact mechanism(s) of antimalarial activity of the artemisinins remains under investigation it is clear that the presence of endoperoxide moieties within the active forms of these molecules is an essential requisite for the antiparasitic effect. Evidence for this is provided by the lack of antimalarial activity of deoxyartemisinin, which is a derivative that lacks the endoperoxide bridge moiety.

During the part of the life cycle of *P. falciparum* that occurs within human erythrocytes, the parasite uses haemoglobin as a food source. Haemoglobin is imported into acidic food vacuoles and broken down by proteolytic enzymes (plasmepsins) and cysteine proteases (falcipains) to amino acids. The process generates haem, which is detoxified by conversion to an insoluble compound known as malaria pigment or haemozoin. However, the haem also provides the ferrous iron that activates the endoperoxide bridge moiety in artemisinin molecules to form cytotoxic free radicals. Subsequently, covalent bonds are formed that alter the function of some essential parasite proteins such as membrane transporters.

For many years experts in the field reported no apparent resistance of malaria parasites to the artemisinins. However, a study published in New England Journal of Medicine (NEJM) (December 2008) reported that 2/60 patients who received artesunate alone to treat *P. falciparum* were classified as having artemisinin-resistant infection due to:

- Re-emergence of parasitaemia between Day 21-28
- Prolonged parasite-clearance times (133 and 95 hours versus a median of 52.2 hours for patients who were cured) despite plasma drug concentrations after the first dose that were “adequate” (> mean for cured patients minus 1 SD)
- IC₅₀ for DHA up to 4 times the geometric mean for cured patients and almost 10 times that for the reference clone W2. Resistance did not appear to be mediated by the number of copies of the *P. falciparum* multidrug resistance gene *pfmdr1* or selected *PfATPase6* polymorphisms.

In July 2009 a Lancet article reported on reports of high failure rates associated with ACT in specific areas of Cambodia and Thailand. Clinical artemisinin resistance seems to have emerged along the Thai–Cambodian border from around 2005 onwards. Efforts are being made to try to prevent the spread of artemisinin-resistant strains outside of this region. Also in July 2009 an article was published in the NEJM on the issue of resistance to the artemisinins as observed in two open-label, randomised trials that compared oral artesunate 2 mg/kg for 7 days with a dose of 4 mg/kg for 3 days plus two doses of mefloquine (total 25 mg/kg) for treatment of uncomplicated *falciparum* malaria in Western Cambodia and in Northwest Thailand. Based on detailed study of 40 patients at each location, the median parasite clearance times were 84 h and 48 h in respective sites. Recrudescence (PCR-confirmed) occurred in 6/20 (30%) receiving artesunate monotherapy and 1/20 (5%) receiving artesunate–mefloquine in Cambodia compared with 2/20 (10%) and 1/20 (5%) in Thailand.

The differences were not explained by age, artesunate or DHA PK, in-vitro sensitivity tests or putative molecular correlates of *P. falciparum* drug resistance (relating to the *PfMDR1* or *PfSERCA* genes). It was concluded that *P. falciparum* has reduced in-vivo susceptibility to artesunate in Western Cambodia compared with Northwest Thailand that results in slow parasite clearance.

The most common adverse effects associated with the various orally-administered artemisinin derivatives are nausea, vomiting, bowel disturbance, abdominal pain, headache and dizziness. Mild and reversible haematological and electrocardiographic abnormalities, such as neutropenia and 1st-degree heart block, may be observed infrequently. Neurotoxicity, principally in the form of brainstem lesions, was first identified in animals receiving high doses over long periods. Neurological side-effects such as ataxia, slurred speech and hearing loss have also been reported in a small numbers of humans.

Piperaquine

Piperaquine (PQ) was synthesised by the Shanghai Pharmaceutical Research Institute in the 1960s and later developed in France by Rhone-Poulenc in the 1970s. Piperaquine replaced chloroquine as the recommended treatment for *P. falciparum* malaria in China in 1978 and was used extensively for mass prophylaxis and treatment.

PQ is an orally active bisquinoline that is structurally related to chloroquine. It is a highly lipophilic molecule that is practically insoluble in water while the tetraphosphate salt (PQP) is soluble in hot water.

PQ is slowly absorbed (probably due to its high lipophilicity). It has a large volume of distribution at steady state relative to its bioavailability and a long plasma half-life. Clearance is markedly more rapid in children than in adults, reflecting the higher rates of hepatic metabolism and/or biliary excretion in children. The long half-life and large molecular size/weight suggest that PQ may undergo enterohepatic recycling.

PQ has a similar mechanism of action as chloroquine that involves inhibition of haem detoxification by the parasite. There have been several reports of low rates of cross-resistance between chloroquine and piperaquine. Nevertheless, high rates of resistance to piperaquine have been reported from areas where it has been used alone, especially in China.

About the product

The development of **Eurartesim** builds on the available experience with **Artekin** (and the paediatric size tablets named **Eurartekin**). Both are provided as fixed dose combination (FDC) film-coated tablets of DHA and PQP. Artekin was first approved in China and has subsequently been 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 not identical to that for Artekin but the applicant has proposed that the two are sufficiently similar that pharmacokinetic, safety and efficacy data generated with the one formulation can be extrapolated to the other. It should be noted that *in-vitro* data suggest that co-exposure of *P. falciparum* to DHA and PQ results in a similar phenomenon of inhibition of DHA accumulation in erythrocytes as seen with chloroquine. It has also been suggested that DHA could inhibit uptake of PQ. However, these *in-vitro* observations do not necessarily predict what might occur in the infected patient at clinical doses.

Proposed indication (from the applicant):

Eurartesim is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more.

Consideration should be given to official guidance on the appropriate use of antimalarial agents.

Proposed posology and method of administration (from the applicant):

Posology

Eurartesim should be administered over three consecutive days for a total of three doses taken at the same time each day.

Dosage

Dosing should be based on body weight as shown in the table below.

Table 1

| Body weight (kg) | Daily dose (mg) | | Tablet strength and number of tablets per dose |
|------------------|---|-----|--|
| | PQP | DHA | |
| 5 to <7 | 80 | 10 | ½ x 160mg / 20mg tablet |
| 7 to <13 | 160 | 20 | 1 x 160mg / 20mg tablet |
| 13 to <24 | 320 | 40 | 1 x 320mg / 40mg tablet |
| 24 to <36 | 640 | 80 | 2 x 320mg / 40mg tablets |
| 36 to <75 | 960 | 120 | 3 x 320mg / 40mg tablets |
| 75 to 100 | 1,280 | 160 | 4 x 320mg / 40mg tablets |
| >100 | There are no data on which to base a dose recommendation in patients weighing >100kg. | | |

For patients unable to swallow the tablets, such as infants and young children, Eurartesim may be crushed and mixed with water. The mixture should be used immediately after preparation.

If a patient vomits within 30 minutes of taking Eurartesim, the whole dose should be re-administered; if a patient vomits within 30-60 minutes, half the dose should be re-administered. Re-dosing with Eurartesim should not be attempted more than once. If the second dose is vomited alternative antimalarial therapy should be instituted.

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

There are no data on a second course of treatment.

No more than two courses of Eurartesim may be given within a 12 month period (see sections 4.4 and 5.3).

A second course of Eurartesim should not be given within 2 months after the first course due to the long elimination half-life of piperaquine (see sections 4.4 and 5.2).

Hepatic and renal impairment

Eurartesim has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering Eurartesim to these patients (see section 4.4).

Elderly

Clinical studies of Eurartesim tablets did not include patients aged 65 years and over, therefore no dosing recommendation can be made. Considering the possibility of age-associated decrease in liver and fuction, as well as a potential for heart disorders (see sections 4.3 and 4.4), caution should be exercised when administering the product to the elderly

Paediatric population

See posology table above.

The safety and efficacy of Eurartesim in children aged less than 6 months and in children weighing less than 5 kg has not been evaluated. No data are available for these paediatric subsets.

Method of administration

Eurartesim should be taken orally with water and without food. Each dose should be taken no less than 3 hours after the last food intake. No food should be taken within 3 hours after each dose.

2.2. Quality aspects

2.2.1. Introduction

Eurartesim is presented as conventional immediate release film-coated tablets containing piperaquine tetraphosphate (PQP) (as the tetrahydrate) and dihydroartemisinin (DHA) as active substances in the strength combination of 320 mg/40 mg and 160 mg/20 mg. The other ingredients are pregelatinised starch, dextrin, croscarmellose sodium, hypromellose and magnesium stearate. The film-coating consists of hypromellose, titanium dioxide and macrogol 400. The film-coated tablets are marketed in PVC/PVDC/aluminium blisters (PVC/PVDC/alu) blisters packed in cardboard boxes.

2.2.2. Active substance

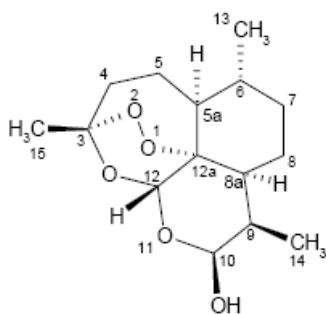
Two active substances are used in this fixed combination product, dihydroartemisinin (DHA) and piperaquine tetraphosphate (PQP).

Dihydroartemisinin (DHA)

Its chemical name is (3R,5aS,6R,8aS,9R,10S,12R,12aR)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-ol according to the IUPAC nomenclature.

DHA consists of colourless needles or a white or almost white, crystalline powder and no polymorphs have been identified. Practically insoluble in water, slightly soluble in acetonitrile and ethanol, soluble in dichloromethane. There are 8 chiral centres in the molecule, which are stereo-configured. It was noted that there are 2 epimers at chiral centre C10 - α (R) and β (S).

Figure 1: Chemical structure of dihydroartemisinin (DHA).



Manufacture

Dihydroartemisinin (DHA) is a semisynthetic compound obtained by reduction of artemisinin extracted from the leaves of *Artemisia annua* L followed by purification and blending. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, catalysts and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The purified active substance is packed in an inner and outer low density polyethylene (LDPE) bag. Both bags are closed with a plastic fastener. The bags are inserted into a high density polyethylene (HDPE) drum, which is closed with a lid equipped with a rubber gasket.

Structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, ^1H NMR spectroscopy, ^{13}C NMR spectroscopy and mass spectrometry. The solid state characteristics were determined by FT-IR, XRPD, ^1H NMR spectroscopy and optical microscopy.

Specification

The active substance (DHA) specification includes tests for physical appearance, identification (IR and HPLC), water content (Karl Fischer), specific rotation (polarimetry), heavy metals (Ph.Eur.), sulphated ash (Ph.Eur.), residual solvents (GC), assay (HPLC), impurities (HPLC), particle size distribution and microbiological limit tests (Ph.Eur.). It was noted that all specifications reflect the relevant quality attributes of the active substance. A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH guidelines. In general analytical methods proposed are suitable to control the quality of the active substance. Impurities have been extensively described, classified as process related impurities and possible degradation products, and qualified with reference to toxicological studies. Data on five production scale batches of DHA have been provided and the requirements in the active substance specification were met.

Stability

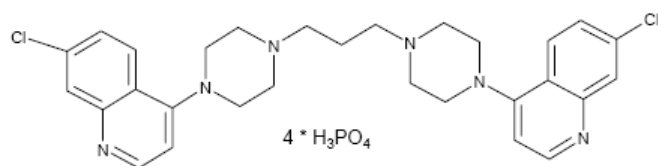
The stability results of clinical batches confirmed the thermal sensitivity of DHA. In this context, the long-term stability studies with commercial batches were conducted at $5^\circ\text{C} \pm 3^\circ\text{C}$.

The stability results from long-term ($5^\circ\text{C} \pm 3^\circ\text{C}$.) and accelerated studies ($25^\circ\text{C} \pm 2^\circ\text{C} / 60 \pm 5\%\text{RH}$) were completed according to ICH guidelines. The following parameters were monitored during the stability studies: appearance, water content, specific rotation, assay and related substances. Forced degradation studies and photostability studies were conducted and it was noted that DHA is thermal, photo and chemical stress sensitive. The results of the long-term studies fulfil the proposed specification and for that reason support the proposed retest period when the active substance is stored in the original packing material and stored under refrigeration at $5^\circ\text{C} \pm 3^\circ\text{C}$ prior to manufacture of the finished product.

Piperaquine tetraphosphate (PQP)

Its chemical name is 4,4'-(propane-1,3-diyl)dipiperazine-4,1-diylbis(7-chloroquinoline) tetrakis (phosphate) according to the IUPAC nomenclature. PQP is an off-white or pale yellow crystalline powder. This active substance is slightly soluble in water and practically insoluble in ethanol, methanol, glycerol, THF, acetonitrile and dichloromethane. This active substance has no chiral centres.

Figure 2: Chemical structure of Piperaquine tetraphosphate. (PQP)



Manufacture

The chemical synthesis of this active substance (PQP) takes place in three steps followed by purification (recrystallisation). The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, catalysts and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The purified active substance is packed in an inner and outer low density polyethylene (LDPE) bag. Both bags are closed with a plastic fastener. The bags are inserted into a high density polyethylene (HDPE) drum, which is closed with a lid equipped with a rubber gasket. Structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, ^1H NMR spectroscopy, ^{13}C NMR spectroscopy, elemental analysis, X-ray powder diffraction and ESI(+) mass spectroscopy. The results of the elemental analysis are consistent with the proposed molecular formula.

Specification

The active substance (PQP) specification includes tests for appearance, identification (IR and HPLC), water content (Karl Fischer), phosphate (Ph.Eur.), heavy metals (Ph.Eur.), pH (potentiometry Ph.Eur.), residual solvents (GC), assay (HPLC), impurities (HPLC, LC-MS), particle size distribution and microbiological limit tests (Ph.Eur.). It was noted that all specifications reflect the relevant quality attributes of the active substance. A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines. In general analytical methods proposed are suitable to control the quality of the active substance. Impurities have been extensively described, classified as process related impurities and possible degradation products, and qualified with reference to toxicological studies. Data for one production scale batch and five small scale batches of PQP have been provided and the requirements in the active substance specification were met.

Stability

Forced degradation studies were performed exposing active substance samples to acidic, alkaline, oxidising conditions; thermal stress on solid sample, aqueous solution at 90°C , humidity and photostability (exposure to visible and UV light). According to the results PQP is stable under alkaline conditions and resistant to thermal stress and humidity. Under acidic conditions, a decrease in assay was noted; several unknown impurities formed together with the known hydrolysis products and other known and unknown impurities. Under oxidising conditions PQP degraded. Some known hydrolysis products and other known impurities were observed when PQP is in aqueous solution at 90°C for 5 hours. Exposure of PQP to light results in coloration of the powder. However, no substantial changes in the assay of PQP and its related substances could be observed.

The stability results from long-term ($25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \pm 5\%\text{RH}$) intermediate ($30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65\% \pm 5\%\text{RH}$), and accelerated studies ($40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\%\text{RH}$) for one clinical trial batch were completed according to ICH guidelines demonstrated adequate stability of the active substance. There was a need to change the manufacturing process several times since the manufacturing process was transferred to a new site. Therefore, three different stability studies were conducted, according to ICH guidelines, using 3 different batches for each stability study. The stability results from long-term ($30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65\% \pm 5\%\text{RH}$) and accelerated studies ($40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\%\text{RH}$) were completed according to ICH guidelines and demonstrated adequate stability of the active substance. Based on the stability data, it can be concluded that the active substance is stable when stored in the original packing material. The results support the agreed re-test period without specific storage conditions.

2.2.3. Finished medicinal product

Pharmaceutical Development

All information regarding the choice of active substances and the excipients are sufficiently justified.

The development of Eurartesim film-coated tablets was based on the formulation and dosage form developed for the Chinese market. The excipients selected for this formulation are commonly used in pharmaceutical formulations. The Applicant decided to develop two strengths of Eurartesim film-coated tablets (piperaquine tetraphosphate (PQP) and dihydroartemisinin (DHA) in the strength combination of 320 mg/40 mg and 160 mg/20 mg). One pilot batch per strength for clinical trials was manufactured from the same compression mixture. Later on in the development phase one additional tablet strength, specific for the infant population corresponding to half paediatric strength 80 mg/10 mg was considered. This third presentation has the same qualitative composition as the other tablets and allows an improvement in the administration compliance and dispensing as well as a lower variability of dosage. However, this strength was not authorised since there is no clinical and safety data available for target paediatric subsets (< 6 months and in children weighing <5kg). It was noted that the film-coating was changed during the pharmaceutical development. However, it was verified that the film-coating does not have an impact on the physical properties of tablets or on their dissolution profile. In other words, this change does not have an impact on the formulation quality or performance.

Manufacture of the product

The proposed commercial manufacturing process involves standard technology and it is divided into 7 main steps: wet granulation, drying phase, sizing/sieving, final mixing, tableting, coating and packaging.

Furthermore, the equipment used is commonly available in the pharmaceutical industry. The critical steps in the manufacturing process have been identified and controlled.

The manufacturing process has been adequately validated for three commercial batches and the results of the manufacturing validation reports were considered satisfactory.

Product specification

The product specification is standard for tablets and contains tests with suitable limits for appearance, identification (HPLC, UV, colorimetric), identification titanium dioxide, assay of PQP (HPLC), assay of DHA (HPLC), impurities (HPLC), PQP uniformity of dosage (Ph.Eur), DHA uniformity of dosage (Ph.Eur),

water content (Karl Fischer), PQP dissolution, DHA dissolution, average mass, residual ethanol (GC), microbial contamination (Ph.Eur).

Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Their limits are justified by reference to stability studies.

All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.

The batch analysis results show that the medicinal product can be manufactured reproducibly and in accordance with the agreed finished product specifications.

Stability of the product

A stability study was conducted an early stage of pharmaceutical development on the clinical batches of Eurartesim for two initial strengths (i.e. adult - 320 mg/40 mg and paediatric - 160 mg/20 mg) packaged in the material proposed for marketing. The stability studies were conducted under long term conditions ($25^{\circ}\text{C}\pm 2^{\circ}\text{C}/60\%\pm 5\%\text{RH}$), intermediate conditions ($30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\%\pm 5\%\text{RH}$) and accelerated conditions ($40^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$) under ICH conditions. The following parameters were investigated: appearance, assay PQP and DHA, impurities, disintegration test, microbial limits. The results the stability studies fulfil the proposed specification. Once the final formulation was defined, more stability studies were conducted on three different batches for each of the Eurartesim strengths. In this context, stability studies were conducted under long-term conditions ($25^{\circ}\text{C}\pm 2^{\circ}\text{C}/60\%\pm 5\%\text{RH}$), intermediate conditions ($30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\%\pm 5\%\text{RH}$) and accelerated conditions ($40^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$) under ICH conditions relevant to Climatic Zones I and II. It was noted that all the stability batches were packed in the same material intended for marketing of the finished product. Results of the stability studies are within specifications for long-term conditions ($25^{\circ}\text{C}\pm 2^{\circ}\text{C}/60\%\pm 5\%\text{RH}$) and intermediate conditions ($30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\%\pm 5\%\text{RH}$).

It was noted that a forced degradation study has also been conducted on one batch per strength of the finished product (high temperature and relative humidity). The results of a thermal stress stability study confirm that DHA is sensitive to temperature when it is combined with PQP. One batch per strength was stored under ICH photostability conditions and no significant changes were observed. It can be concluded that the finished product is not affected by exposure to light. Based on the available stability data relevant to ICH Climatic Zones I & II, the proposed shelf life and storage conditions as stated in the SmPC are considered to be acceptable when the medicinal product is stored and used within the EU.

In accordance with current EU data requirements no stability studies have been provided under (WHO) Climatic Zones III & IV. Therefore, if the medicinal product is stored and used outside the EU, or in any country where the climatic conditions are not represented by ICH climatic zones I & II, it cannot be assumed that the above-mentioned shelf life and storage conditions will apply.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

The pharmaceutical development of the formulation, the manufacturing process, control of the active substances and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The manufacturing flow-chart was provided with

suitable in-process controls. The manufacturing process is adequately validated for three commercial batches at the proposed manufacturing site. The routine specifications and tests methods proposed for the finished product will adequately control the quality of the finished product. Analytical methods were well described and validated in agreement with relevant guidelines.

Batch analyses were presented and the results showed that the finished product meets the specifications proposed.

The container-closure system was found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline (climatic zones I and II). The control tests and specifications for the finished product were adequately established.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished products have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the medicinal product should have a satisfactory and uniform performance in the clinic when stored and used within the EU. At the time of the CHMP opinion, all quality issues have been resolved.

2.3. Non-clinical aspects

2.3.1. Introduction

The majority of the studies conducted were performed in accordance with GLP. The following were not conducted in accordance with GLP: 4 out of 14 of the pharmacokinetic studies; the hERG assay; the 2-week repeated dose toxicity study in the rat; the single dose toxicity studies for qualification of the DKA and DOA degradation products.

2.3.2. Pharmacology

In the treatment of malaria, both DHA and PQP have well established clinical therapeutic usage as does the combination of both compounds (DHA/PQP). As such additional specific non-clinical pharmacology studies were not deemed necessary for Eurartesim. The pharmacological data for DHA, PQP and the DHA/PQP combination are provided from the available literature.

Primary pharmacodynamic studies

DHA is the active metabolite of artesunate and artemether, which are both artemisinin-derived anti-malarial drugs. Typical of artemisinins, DHA has a very short plasma half-life of approximately 1 hour, and therefore, its use as monotherapy requires a multiple dosing regimen of seven days duration.

PQ is structurally related to chloroquine with a similar mechanism of action through the chemical inhibition of parasite haem detoxification. PQ is reported to have a very prolonged half-life (20-22 days in humans), and hence facilitates a shorter treatment regimen.

Eurartesim has been developed combining two drugs with different complimentary half-lives, one short and one long allowing a dosing regimen of 3 days duration while avoiding the recrudescence normally associated with short-course therapy. In addition DHA is stated to be rapidly effective against 95% of the parasite population leaving the PQP with only a few parasites with a very low risk of resistance to eliminate, thus reducing the emergence of Eurartesim resistant strains.

Secondary pharmacodynamic studies

No non clinical studies providing data on secondary or general pharmacology of the DHA/PQP combination product were conducted. This is considered to be acceptable in view of the clinical experience of the two compounds as well as their combination.

Safety pharmacology programme

DHA - Potential Neurotoxicity

The potential for neurotoxicity has been well documented. In animals, neurotoxicity is related to the dose, the route of administration and the pharmacokinetic properties of the different DHA pro-drugs. Sustained CNS exposure from slowly absorbed or eliminated artemisinins is considerably more neurotoxic than intermittent brief exposure. Thus, the oil-based intramuscular (IM) artemether and arteether appear more neurotoxic than those given orally.

Two reviews on artemisinin derivative neurotoxicity concluded that the prolonged presence of artemisinins from the oil-based, intramuscular formulations was the main cause of the observed neurotoxicity in laboratory animals. Other neurotoxic factors were the high doses of artemisinin compounds used in animal studies and the different pharmacokinetic profiles following different routes of administration.

The potential neurotoxicity in man of orally administered DHA, (the active metabolite of the majority of artemisinin derivatives) was concluded to be highly unlikely given the rapid clearance of DHA and the short exposure (3 days of treatment). These conclusions are also consistent with those of the WHO Informal Consultation on Clinical Neurological Investigations Required for Patients Treated with Artemisinin Compounds and Derivatives 1998.

DHA- QT Prolongation

In studies with artemether and arteether ECG effects have been noted: prolongation of QTc and changes on ECG with bizarre ST-T segment changes in rats and dogs administered artemether. Further studies in rat (12.5-50mg/kg/day for 28 days) confirmed ECG changes. Both IM and PO exposure to artemether at high dose levels was associated with a prolongation of mean QT interval of ECG in dogs. In dogs given 50mg/kg/day of artesunate, by IV route, for 14 days, no ECG changes were observed.

The applicant states that cardiovascular sinus bradycardia and a reversible prolongation of the QT interval have been reported (Meyler's Side Effects of Drugs; SEDA-21, 293) with artesunate. The applicant further states that in WHO monographs such adverse effects from extensive clinical trials were not reported.

PQP Cardiovascular Effects

In a recent publication it was reported that in rabbits, acute cardiovascular toxicity of PQP was compared with that of chloroquine by determining the cumulative intravenous dose that caused a fall in blood pressure, or electrocardiographic abnormalities. Using this determination, it was observed that, in general, PQP had a better cardiovascular toxicity profile than chloroquine.

A *h*ERG study was carried out for PQ as part of the investigation into the QTc prolongation potential of PQ. This is to support the extensive analyses performed in the clinical studies. This study (0083-2009) was carried out by Sigma-tau to assess the effect of the antimalarial drugs chloroquine (CQ), PQ and mefloquine (MQ) on *h*ERG tail current. Exposure to CQ, PQ and MQ reduced *h*ERG residual tail current in a dose related manner and the dose response curves for the test items gave IC values of 5.28, 4.03 and 19.88µM, respectively. All the test items decreased IKr in a dose related manner; CQ and PQ had nearly identical *h*ERG IC50 values, suggesting a similar potential interference on cardiac repolarization.

DHA/PQP

As a result of the above data from literature, the applicant states that the cardiovascular (CVS) and central nervous system (CNS) effects have been specially monitored in the clinical trials.

Targeted CNS exploration during the clinical trials was stated not to reveal any abnormalities.

An evaluation of the torsadogenic risk of DHA and PQP in response to a question during assessment of the dossier revealed that although there was such a risk, it was lower than for CQ and halofantrine and in the same range as for MQ and lumefantrine. The torsadogenic risk indices of anti-malarial drugs were evaluated as ratios between IC₅₀ values obtained in the *h*ERG study and the free therapeutic plasma concentrations (FTPC) in patient studies, higher risk being associated with lower ratio value. For this ratio, the IC₅₀ values derive from the study at 37°C (Zenas/Craven AS 2009-1).

For comparison, additional antimalarial drugs were evaluated in the *h*ERG assay by Zenas/Craven (AS 2009-1), as reported in Table hereafter.

Table 2: Torsadogenic risk index (ratio A/B) of antimalarial drugs with respect to the free therapeutic plasma concentration (FTPC)

| Drug | <i>h</i> ERG IC ₅₀ (μM)* A | FTPC (μM) B | Ratio A/B |
|--------------|---|-------------------|--------------|
| DHA | 9.62 | 0.24 | 40.1 |
| PQP | 0.182 | 0.00828 | 21.9 |
| Chloroquine | 0.96 | 0.41 [#] | 2.34 |
| Mefloquine | 1.03 | 0.05 [#] | 20.6 |
| Lumefantrine | 2,578 | 0.17 [#] | 15.16 |
| Halofantrine | 0.018 | 0.57 [#] | 0.03 |

* from Zenas/Craven electrophysiology study AS 2009-1.

[#] from Traebert et al., 2004.

The risk that DHA and PQP might induce Torsade de Pointes arrhythmias exists, but according to this analysis the ratios for DHA and PQP are higher or in the same range than those for the other antimalarial compounds tested (chloroquine, mefloquine and lumefantrine).

Also, the association of DHA and PQP did not produce *h*ERG inhibition greater than that of the single compounds.

According to ICH S7B guidelines, cardiovascular safety was assessed by using the *h*ERG assay. No indication of particular cardiovascular problems related to QT prolongations was evidenced after Eurartesim administration during the dog toxicity studies (see further- repeat toxicity studies).

In human subjects, QT prolongation was reported after DHA plus PQP administration (Karunajeewa et al., 2003; Mytton et al., 2007).

The applicant's conclusion from the electrophysiology findings was that DHA/PQP does not cause clinically relevant cardiotoxicity. The QTc prolongation observed was stated to be comparable with that observed with other antimalarials, including drugs with no known cardiac effects, which suggests that QT prolongation may have resulted from recovery from malaria and be unrelated to drug treatment. However, the issue of the effect of DHA/PQP on QTc prolongation and the risk of cardiac arrhythmias required further exploration. The CHMP requested additional non-clinical *in-vitro* experiments to further elucidate:

- The arrhythmogenic and torsadogenic potential of Eurartesim
- The underlying mechanisms of the observed QT prolongation and
- Whether a pharmacodynamic interaction exists between PQP and DHA.

The applicant submitted the following four studies:

- Trafficking of *h*ERG channels
- Effects on cardiac IKs current
- Effects on cardiac INa current
- Isolated perfused rabbit left ventricular preparation

In addition the applicant submitted 12 references from the published literature and an expert overview.

Block of *h*ERG currents does not seem to be primarily responsible for the marked QT interval prolongation observed in humans after administration of Eurartesim.

An inhibition of the trafficking of *h*ERG channels by drugs has recently been identified as an important mechanism for several torsadogenic drugs, but both DHA and PQP at clinically relevant concentrations were shown to have no effects on *h*ERG channel trafficking in HEK 293 cells.

A block of the cardiac slow delayed rectifier K^+ current (I_{Ks}) may also be ruled out as a mechanism for the marked QT interval prolongation induced by Eurartesim, since neither DHA, PQP nor the combination of both had marked effects on I_{Ks} in isolated human atrial myocytes. Also, for artemether/lumefantrine and chloroquine no such effect was observed.

A protective mechanism against the induction of TdP arrhythmias resulting from the block of cardiac I_{Na} can be excluded, since neither DHA, PQP nor the combination of both had effects on peak I_{Na} in isolated human atrial myocytes. Such an effect was neither observed for the combination of artemether/lumefantrine, However, chloroquine (10 μ M) blocked cardiac I_{Na} by about 43%.

In the isolated perfused rabbit left ventricular preparation, DHA did not show any torsadogenic effects, but shortened the QT interval and Tp-e (an index of transmural dispersion of repolarisation and proarrhythmias including early afterdepolarisation) at high concentrations of 30 and 100 μ M (which may indicate some protective effects against the induction of TdP arrhythmias). In contrast, PQP concentration-dependently increased APD₉₀, QT interval and Tp-e at clinically relevant nanomolar concentrations and increased the TdP score at 3 μ M. However, PQP did not induce early afterdepolarisations [EADs], an important surrogate parameter for the induction of Torsades de Pointes [TdP] arrhythmias) even at a high concentration of 3 μ M, about 1,000-fold higher when compared to therapeutically effective free plasma concentrations of PQP. Similar effects on electrophysiological parameters to those of PQP alone were obtained when PQP was combined with a low concentration (2.4 μ M) of DHA, but the effects of PQP on these parameters were less when combined with DHA at concentrations much higher than those achieved in humans (7.2 μ M). These observations indicate that PQP has a torsadogenic potential, which is lower than that of chloroquine but higher than that of artemether/lumefantrine.

Pharmacodynamic drug interactions

No non-clinical data relating to pharmacodynamic drug interactions were obtained.

2.3.3. Pharmacokinetics

The pharmacokinetics of both DHA and PQP are detailed in the literature. In addition, in-house studies were performed by Sigma-tau to evaluate the pharmacokinetic profile of piperaquine (PQ) after single and repeated administration of DHA/PQP in rats and dogs. The systemic exposure to PQ in rats in dogs was assessed during 4-week toxicity studies. Absorption-distribution-metabolism-excretion (ADME) and protein binding studies in rats were also performed using [¹⁴C]-PQP (co-administered with DHA).

In toxicology and pharmacokinetic studies, analyses of PQ in rat and dog plasma and DHA in dog plasma were carried out using validated HPLC-MS/MS methods. However, due to the instability of DHA in dog plasma during freeze-thaw cycles, the DHA toxicokinetics in dogs were not assessed.

In single-dose testing in male rats, systemic exposure following a single oral administration of DHA/PQP at the dose of 270mg/kg (30mg/kg of DHA and 240mg/kg of PQP) using three different formulations revealed that the PQ pharmacokinetics were characterised by a slow absorption and

elimination rate; the maximum plasma concentration was reached about 8 to 13 hours after treatment, and the apparent elimination half-life was ~ 200 hours for each formulation.

In the 5 day oral pharmacokinetic study in Beagle dogs, in which DHA/PQP was given by the oral route at 22.5mg/kg/day (2.5mg/kg of DHA and 20mg/kg of PQP), 45mg/kg/day (5mg/kg of DHA and 40mg/kg of PQP) in 5% methocel, the daily systemic exposure to PQ increased substantially after both dose levels in direct proportion with the dose without gender difference. After repeated administrations an accumulation ratio of about 5 based on AUC_{0-24h} values, was observed. The PQ apparent elimination half-life evaluated was ~ 70-210 hours.

The in vitro plasma protein binding of PQ evaluated in rat, dog and humans suggested that the binding of PQ to plasma proteins could be considered virtually complete (>99%).

An in vivo study performed in rats to assess the tissue and organ distribution of total radioactivity after a single oral dose of 80mg/kg [¹⁴C]-PQP and 10mg/kg of DHA indicated an extensive distribution of [¹⁴C]-PQ. About 36% of the administered dose was still found in the body 168 hours after administration both in male (albino and pigmented) and female rat. Apart from the gastrointestinal tract, the highest concentrations of the radioactivity were measured in adrenal glands, bone marrow, lachrymal glands, liver, lungs pituitary and spleen. High levels of radioactivity were also measured in ovaries of the female rats. Overall, there was no qualitative gender difference in distribution of the radioactivity. Concentrations of radioactivity in blood were higher than in plasma suggesting that an association of radioactivity with blood cells occurred.

In the pigmented rats the maximal level of radioactivity in the eyes was approximately tenfold higher than in the albino rats, indicating a significant binding of [¹⁴C]-PQ to melanin-containing tissues.

The autoradioluminography of the whole uterus of the pregnant animals showed a distribution of radioactivity in the fetuses, mainly concentrated in the foetal liver, indicating a placental transfer after administration.

The metabolite profile of PQ in human hepatocytes was not affected by the co-incubation of DHA. PQ was the main compound detected after 2 hours incubation with mouse, dog and human hepatocytes, accounting for 75-89% of total drug-related material. Conversely, with rat hepatocytes unchanged PQP accounted for only 7%. PQ was mainly metabolized through oxidation. Four mono-oxidated metabolites were detected. M1 was the main metabolite in rat and mouse, accounting for 75% and 14% of total drug-related material, respectively. M3 was the main metabolite in dog and humans accounting for 7% and 9%, respectively. This metabolite has already been identified in humans in vivo. In addition, M10, M2 and M4 were present in low amounts (up to 3%). M4 was detected only in the dog.

No phase II metabolites of PQ were detected in any species.

DHA is the main active metabolite of artesunate. When administered intravenously to male rats [¹⁴C]DHA was converted principally to the biologically inactive α -DHA- β -glucuronide (α -DHA-G). DHA is also eliminated in bile as minor glucuronides of nonendoperoxide isomers, namely tetrahydrofurano acetate and 3-hydroxydesoxy rearrangement product.

Studies using human liver microsomes showed that [³H]DHA-G was the only detectable metabolite of [³H]DHA. From an in vitro study (Ilett et al 2002) it was verified that the main UDP-glucuronosyltransferases (UGTs) involved in the DHA metabolism in humans were UGT1A9 and UGT2B7.

In a mass balance study following a single dose of 90mg/kg of [¹⁴C]PQP/DHA combination product to male and female rats the recovery of the total radioactivity within 720 hours after administration accounted for approximately 97.5% of the dose in both genders. About 80% of the dose was eliminated in faeces, while the urinary excretion accounted for about 4% of the dose. Approximately

46% of the dose was eliminated in faeces within the first 24 hours. At the end of the collection period of excreta (720 hours) about 13% of the dose was recovered from the carcasses.

After administration to male rats, the radioactivity in whole blood reached the maximal concentration within 24 hours post-dosing. The radioactivity in blood was detectable up to 720 hours, resulting in an average apparent terminal half-life of 222 hours.

In plasma, the maximal radioactivity concentration was achieved at 3 hours post-dosing. Detectable levels of radioactivity were measured up to 24 hours post-dosing.

The half-life of piperaquine in plasma was similar to that of total radioactivity in blood, indicating that both concentrations declined in parallel.

In blood, plasma and milk, mean maximal concentrations of radioactivity were achieved 24, 3 and 6 h post dosing respectively. After the peak, blood and milk concentrations seemed to decline in parallel, whilst the decay of the plasma concentrations seemed to be faster than those in blood and milk. In milk, the maximal concentration of total radioactivity was attained 6 h post-dosing, indicating a rapid distribution. In terms of AUC, total radioactivity in milk was two and seven times higher than those in blood and plasma, respectively. Overall, the systemic exposure values indicated a rapid and extensive distribution of total radioactivity in milk. In addition, relevant and time-dependent distribution of total radioactivity into red blood cells was observed.

Three toxicology studies contributed additional pharmacokinetic data regarding PQ and the conclusions are outlined below.

Following repeated oral dosing of DHA/PQP in male and female rats (90 and 270mg/kg/day over 14 days) the PQ plasma concentrations were found to be quite "flat" over the 24 hours observed following last dose administered. Due to the long T_{1/2} observed in rats, PQ accumulated in plasma after multiple dosing. No gender differences were observed. C_{max} and AUC_{0-24h} values of PQ increased linearly, but without a clear proportionality with the dose in the dose range investigated.

After single and repeated administrations of DHA/PQP during the 4-week toxicity study in rats, no relevant gender differences were observed in the PK of PQ. On Day 1, systemic exposure to PQ did not deviate substantially from dose proportionality. After repeated oral administrations at all doses, detectable concentrations of PQ were measured up to the end of the experiment (360 h post last dosing). Systemic exposure increased with the dose in the dose range investigated. Average accumulation ratio, based on AUC_{0-24h} values, was in the range 2-4, suggesting accumulation after repeated administrations.

During the 4-week toxicity study in dogs, no relevant gender differences were observed in the PK of PQ. After single oral administration of DHA/PQP at 22.5mg/kg dose, dogs were exposed to PQ levels below the limit of the quantification of the analytical method (10ng/mL). At the other two doses, 90 and 180mg/kg, the systemic exposure to PQ increased rather in direct proportion to the dose.

Following 27 days of repeated oral administration of PQP/DHA combination product, the animals resulted exposed to PQ at all the three tested doses. Accumulation was observed at 22.5 and 90mg/kg, when the compound was administered daily. Conversely, at 180mg/kg every other day, PQ accumulation was negligible.

In toxicity studies in animals, daily dosing was performed to conservatively evaluate toxicity during repeated exposure over 2 and 4 weeks in rats and 4 weeks in dogs. It should be born in mind that three days of dosing in humans is not too dissimilar to a single dose in pharmacokinetic terms (when one considers exposure in relation to the very long half-life of PQ in adults and children, of about 21-22 days). Eurartesim is not intended for chronic dosing, so animal studies using a chronic dosing regimen should be interpreted with caution.

For the safety factor calculation the cumulative AUC over the entire period of treatment in rats and dogs were compared to the cumulative therapeutic AUC in humans. This analysis shows that at the 30mg/kg/day dose in rat and the 22.5mg/kg/day dose in dogs, the exposure levels in animals exceed those in humans during the clinical dosing regimen. Animals tolerated exposures over of the duration of treatment at Maximum Tolerated Dose (MTD) that were at least 11-17 fold above the human exposure during the clinical dosing regimen.

2.3.4. Toxicology

DHA/PQP and its individual components DHA, PQP and the DHA degradation products ST3463 (DKA) and ST5126 (DOA), have been tested in single-dose and repeat-dose toxicity studies in mice, rats and Beagle dogs. The toxicokinetics of PQP has been determined in rats and in Beagle dogs. The genotoxic potential of DHA and PQP has been assessed in vitro in bacterial reverse mutation assays, but not for chromosomal aberration.

Single dose toxicity

Single doses of 270mg/kg DHA/PQP in rats, and 200mg/kg DHA in mice showed no clinical adverse reactions.

In addition to DHA, the potential toxicity of DKA given alone or in combination with DHA (DHA + 5% DKA) was also assessed. At doses of 100 and 200mg/kg, the combination of DHA and 5% DKA did not cause any adverse clinical reactions. DKA given alone did not show any toxicity at the doses tested.

The potential toxicity of a single-dose of DHA or its degradation product DOA given alone was assessed. DHA and DOA were given to CD-1 male mice as a single oral administration at the doses of 400, 800 and 1200mg/kg each. DHA did not show signs of overt toxicity up to 1200mg/kg. After administration of the high dose of 1200mg/kg, DOA only induced a slight transient hypoactivity.

Repeat dose toxicity

DHA/PQP from 14 to 28 days repeated dosing to rat and Beagle dog.

The five-day repeat-dose oral toxicity study in mice revealed no significant differences in toxicity of DHA, when given alone or in combination with DKA.

In the corresponding study for the qualification of DOA CD-1 male mice were administered doses of 200, 400 or 800mg/kg DHA alone or in combination with DOA (DHA+ 3% DOA) for five days. The low dose of 200mg/kg/day of DHA given alone or in combination with DOA at 6mg/kg/day, under the conditions applied in the present study, was considered the NOEL.

An additional 5 day repeat-dose toxicity study was carried out in Beagle dogs as part of the qualification of DHA degradation products (0487-2008). Animals were administered doses of 45 or 90mg/kg DHA/PQP alone or in combination with 10% DKA+ 3% DOA. The high dose of 90mg/kg/day of DHA/PQP alone or in combination with DHA degradation products, under the experimental conditions applied in the study was considered the NOEL.

In the two-week repeat-dose toxicity study 270mg/kg/day DHA/PQP given to rats was regarded as the MTD. Further increase of the dose to 540mg/kg/day caused acute toxicity to progress to lethal effects, accompanied by decreases in reticulocytes, increases in AST and ALT, and most severe clinical signs in high dose animals. Morphological changes were dose dependent from 90 to 540mg/kg/day and were

mainly characterized by infiltration of macrophages, and by intracytoplasmic deposition of basophilic granular materials in macrophages. These changes were consistent with phospholipidosis.

The results from the 14-day rat study were confirmed in the 28-day rat oral toxicity study at dose levels of 30mg/kg/day, 90mg/kg/day and 270mg/kg/day. The top dose of 270mg/kg/day DHA/PQP was lethal in the week 4 of treatment. 90mg/kg/day of DHA/PQP was considered the MTD.

In the 4-week study one group of animals was treated with chloroquine. Because of early mortality in this group, the dose was reduced from 90mg/kg/day to 30mg/kg/day. Similar infiltration of foamy macrophages was observed, although it was less prominent than with DHA/PQP. Chloroquine also induced morphological changes such as myofibre degeneration mainly in diaphragm and skeletal muscles. These findings were not observed in the DHA/PQP groups.

In a 4-week oral toxicity study 22.5mg/kg/day, 90mg/kg/day, and 180mg/kg/day DHA/PQP (enriched with 5% ST3463) were administered to Beagle dogs. From day 8 onwards, 180mg/kg was only administered every second day. Animals being treated with 180mg/kg every second day showed similar adverse reactions to those treated with 90mg/kg/day. The main findings in 90mg/kg/day treated animals were some sporadic variations in clinical characteristics such as a decrease in activity or food intake, some variations in clinical chemistry (decrease in albumin or increase of globulin and cholesterol) and the appearance of foamy macrophages in various organs. Consistently, all repeated dose toxicity studies showed morphological alterations in a dose dependent manner. The 22.5mg/kg dose was regarded to be the NOAEL.

Phospholipidosis was observed after administration of PQP in all repeat-dose toxicity studies and is a well known morphological finding from preclinical studies with cationic amphiphilic drugs. Chloroquine is a cationic amphiphilic drug, which can also induce formation of lamellar bodies in cells. It has been suggested that the induction of lamellar bodies, and phospholipidosis, respectively, are independent of toxicity. Indeed, phospholipidosis has been observed in cells without signs of toxicity. Phospholipidosis does not seem to be predictable with regard to severity and incidence, but lipid composition of the cells affected and half-life or potential for accumulation may determine the likelihood of phospholipidosis.

The prolonged pharmacological effect of PQP may account for the higher level of phospholipidosis in animals treated with PQP at 270mg/kg compared to those treated with chloroquine at a dose of 90mg/kg.

No significant differences were observed between PQP and chloroquine treated animals at 90mg/kg. Observations in chloroquine treated animals such as the presence of inclusion bodies in the cornea epithelium, and opacities in the lens of the eyes, have not been observed in PQP treated animals in the current studies.

The applicant provided a profound discussion on the deaths observed in dogs and rats in the repeated dose toxicity studies. Mortality data and the results of post-mortem examination obtained in toxicity studies after administration of DHA/PQP for 2 or 4 weeks in rats and for 4 weeks in dogs, have been thoroughly reviewed. This review indicates that (i) the death of a dog was probably induced by poor general condition and intestinal symptoms; and (ii) the death of the rats at the highest dose level (270 mg/kg) was most probably the result of very poor condition due to the accumulation of PQP in almost all the tissues. Moreover, there was no evidence that the cause of these deaths was linked to either cardiotoxicity or neurotoxicity.

Genotoxicity

The genotoxic potential of PQP, DHA, DKA and DOA was studied in four *Salmonella typhimurium* reverse mutation assays. It was demonstrated that neither DHA nor PQP or DKA have any mutagenic potential in the bacterial mutation assays performed. In response to questions concerning the potential genotoxicity of the above compounds, the applicant re-evaluated all the historical data. The applicant also conducted, with DHA and PQP, in vitro chromosomal aberration assays in human lymphocytes and micronucleus tests in rat and in CHO cells. When considered together, the data demonstrate that DHA and PQP are not genotoxic.

Carcinogenicity

No data is available in the literature on the carcinogenicity of DHA or PQP or the combination. As treatment is only intended to be given for three days, carcinogenicity tests are not required.

Reproduction Toxicity

Concerning reproductive toxicity, non-clinical data on the effects of DHA in pregnancy is available in the literature and no further non clinical studies were deemed necessary. DHA/PQP is to be administered according to WHO 2006 guidelines. The applicant states that they are conducting studies to assess the use of DHA/PQP in pregnant women.

There is non-clinical data on reproductive toxicity available on the effect of PQP from recently completed studies carried out by Sigma-tau. The final reports from these studies have now been made available which show that PQP did not show any teratogenic effects in rats or rabbits when treated with a dose of 80mg/kg during the embryofoetal stage (GD6 to GD17) or in the rat when treatment was continued through gestation until the first day of parturition (GD6 to GD21). PQP also did not affect the course of pregnancy. In the rabbit Segment II study (0140-2008) no plasma levels of PQ were detected at dose levels below 80mg/kg. The applicant provided a plausible explanation for this finding. There was no effect of PQP on delivery at doses below 80mg/kg in rats. However in animals receiving either an interrupted treatment of 80mg/kg or continuous treatment some effects were observed. These animals exhibited prolonged gestation, altered modality of delivery and increased perinatal mortality. Individual variation was observed with some animals delivering normally and others showing complications. Of the animals who delivered normally, PQP did not interfere with lactation or pup growth (body weight gain). Food consumption, behavioural development or sexual maturity up to weaning was also unaffected, even when pups were exposed to PQP during the suckling period.

The role of embryonic erythroblasts in the developmental toxicity of artemisinin derivatives has been investigated in vivo in rats (White et al 2006, Longo et al. 2006a), in monkeys (Clark et al 2008a), and in vitro in rat whole embryo culture (Longo et al 2006a, 2006b). This literature has recently been summarized by Clark (2009). The depletion of primitive red blood cells in the embryo is likely a primary cause of developmental toxicity by artemisinins. Antiangiogenic properties of this class of compounds may contribute to their developmental toxicity, although in vitro and in vivo data suggest that effects on angiogenesis occur after effects on primitive RBCs have been observed.

There were no studies in juvenile animals. The applicant states that although children are included in the target patient population, studies on juvenile animals were not deemed necessary, in view of the existing clinical experience in children with the combination. The need for juvenile animal studies has been superseded by clinical experience.

Other toxicity studies

Concerning PQP impurities ST3106, ST3590, ST3593, ST3591, ST3592, ST5701, ST5702 the limits of these impurities has now been tightened to not more than the ICH Q3A/Q3B qualification threshold, except for ST3590. Appropriate qualification studies were conducted on this impurity which can be considered to be toxicologically qualified.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has conducted an ERA for DHA and PQP.

Eurartesim is indicated for the treatment of an orphan condition in the EU. Consequently the default F_{pen} value is assumed to be 0.0005. The share prediction is assumed to be 100%. The applicant was requested to provide a clear explanation as to the provenance of the values used in the calculation of the ERA and to consider the issue of the dosing schedule of Eurartesim.

The applicant asserted that proposed dosing schedule is no more than once a year. Consequently, in the calculation, the following is considered: One treatment per year, and the maximal dose i.e. 4 tablets (320 mg of PQP + 40 mg of DHA) once a day over three consecutive days. The total daily dose is 1,280 mg of PQP and 160 mg of DHA. The total dose for one treatment is 3,840 mg of PQP and 480 mg of DHA. For a total of 8,000 treatments that means per year: 30.720 kg of PQP, that means about 18 kg of PQ and 3.840 kg of DHA. Considering the 20,000 treatments /year (Orphan drug status), 76.800 kg of PQP, or 45 kg of PQ and 9.300 kg of DHA. Whatever the mode of calculation the PECs remain below the limit of 0.01.

According to Wu J. et al, the log K_{ow} for DHA is 2.19. (Wu J et al. 1982). Using the software DEREK, (Derek for Window Ver 12.0.0; Lhasa Ltd), Log K_p calculation is 2.4508. With both sources, the log K_{ow} is below 4.5.

The value of the Log K_{ow} (or Log P) for PQP is 5.8 as fully reported in Report N° CAD-PCPS-ST3073-09-023. Based on the Log K_{ow} value of 5.8, piperazine is being evaluated for persistence, bioaccumulation and toxicity according to the EU TGD. The potential for persistence will be evaluated based on transformation of piperazine in water-sediment systems as per OECD 308. Bioaccumulation potential will be determined based on the fish bioconcentration study following OECD 305. The toxicity of piperazine to aquatic organisms will be determined based on data from the fish early life stage study (OECD 210), the reproductive toxicity to *Daphnia magna* (OECD 211), and toxicity to green alga (OECD 201).

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation to be addressed:

The applicant should submit all the relevant final audited end-of -study reports and an updated overview of the ERA to take into account the new data.

2.3.6. Discussion on non-clinical aspects

Due to the long history, extensive clinical exposure in the target population, as well as data available on PQP and DHA, the traditional battery of formal non-clinical studies has not been performed. The non-clinical studies focused on areas of concern.

Additional studies have been performed as per request by the CHMP (*h*ERG study, further mechanistic studies on QT prolongation, tests evaluating chromosomal damage to have a robust evaluation of

clastogenicity) as well as mandatory tests to qualify impurities/degradation products according to updated specifications.

Neither block of *h*ERG currents, nor inhibition of *h*ERG channel trafficking, nor block of cardiac IKs seem to be responsible for the marked QT interval prolonging effects of Eurartesim observed in humans (see further). The results of the studies in the isolated perfused rabbit left ventricular preparation indicate that the marked QT interval prolongation observed in humans after administration of Eurartesim is primarily caused by the PQP component, although PQP did not induce early-after-depolarisations. The results of these *in vitro* experiments indicate that the torsadogenic potential is low for the PQP component and does not increase when PQP is co-administered with DHA.

Neurotoxicity is a potential risk of artemisinin derivatives, further considered as part of the RMP. However, there was no evidence of DHA-induced lesions in the specific nuclei in rats or dogs, even at lethal dose. Neurotoxicity of orally administered DHA in humans can be considered highly unlikely, given the rapid clearance of DHA and its short exposure.

Experience with DHA demonstrated that DHA has a low toxicity and that the most sensitive index of DHA toxicity is the decrease in reticulocyte count. In the non-clinical studies performed with Eurartesim, no decrease in reticulocyte count was seen which implies, the dose levels given for DHA were not sufficient to achieve toxicity.

As main nonclinical safety findings after repeated dosing of Eurartesim were phospholipidosis and degenerative lesions in numerous organs and tissues. These adverse reactions were seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use. It is not known whether these toxic effects are reversible. Hence, an appropriate statement has been added to section 5.3 of the SmPC.

Information that no reproductive toxicity studies had been performed with the combination of DHA and PQP is also included into section 5.3 of SmPC. Embryotoxic risk in humans is minimised via an SmPC warning (see SmPC section 4.6). Additional risk minimisation measures are planned in this regard (pregnancy registry; educational outreach programme to health care workers).

2.3.7. Conclusion on the non-clinical aspects

Eurartesim cardiovascular effects and the associated clinical findings were concluded to derive mainly from the effects of PQP. As part of the investigation into the QTc prolongation potential of PQP, the applicant submitted data from mechanistic studies. These experiments indicate that the torsadogenic potential of Eurartesim is not as high as expected from the clinical QT studies performed with Eurartesim. However, reference is made to section 3.4 (Clinical) for further discussion of the issue of QTc prolongation.

Reproductive toxicity is a potential concern flagged in the Risk Management Plan (RMP).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The study reports contain statements to the effect that they were conducted in accordance with the World Medical Association Declaration of Helsinki and ICH Topic E6, Guideline for Good Clinical Practice, including the archiving of essential documents.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

GCP inspection

At the time of review of the responses to the Day 120 List of Questions (LoQ) a GCP inspection was triggered. The CHMP endorsed the inspection report on 21 January 2011. The final conclusion was that there were no findings that would preclude acceptance of the safety and efficacy data provided from sponsored studies.

2.4.2. Pharmacokinetics

There were three sponsored pharmacokinetic studies included in the initial application dossier as shown below. The three studies involved administration of **Artekin** (40 mg DHA plus 320 mg PQP [tetraphosphate] = 181 mg free PQ) or **Eurartekin** tablets (20 mg DHA and 160 mg PQP).

Table 3

| Study Type | Study Number | Objective |
|------------|--------------------------------------|---|
| PK Study | ART-DFM-05-002 | Phase I to assess PK of one dose of 40mg DHA and 320mg PQP in healthy volunteers |
| PK Study | ST3073+ST3074 DM04009 ^(a) | Phase I/II to assess PK of 40mg DHA and 320mg PQP in adult patients with malaria after repeated dose |
| PK Study | ST3073+ST3074 DM04008 ^(a) | Phase I/II to assess PK of 20mg DHA and 160mg PQP in paediatric patients with malaria after repeated dose |

(a) ST3073 is the Lab code for PQP

ST3074 is the Lab code for DHA

Plasma concentrations of **DHA** and piperazine (**PQ**) were determined. DHA was measured by LC-MS/MS for which the validated assay had a LLOQ at 10 ng/mL. PQ was measured by LC-MS/MS that could only be validated to 20% at all levels and to 25% at the LLOQ. The validated assay had a LLOQ at 5 ng/mL.

The single dose study in 16 healthy male Caucasian volunteers (**ART-DFM-05-002**) was conducted in Switzerland during 2005 and involved sampling up to Day 90. However, due to the insensitive assay the AUC DHA could not be calculated for 8/16 individuals and PQ was < LLOQ between 12 and 72 h post-dose with the exception of one subject with quantifiable PQ at 96 h post-dose and one at 144 h post-dose.

The study in adults with *P. falciparum* malaria (**DM04-009**) was conducted in Thailand during 2005-2006. The ratio of AUC_{0-t}/AUC_{inf} for DHA was > 90% in all patients and plasma concentrations declined rapidly in a mono-exponential manner. The mean clearance value (1.34 L/h/kg) corresponded to 67 L/h in an adult malaria patient population weighing approximately 50 kg. The mean V_{ss}/F was determined to be approximately 0.8 L/kg, which is about 40 L for a 50 kg individual.

Table 4: Pharmacokinetic Results for DHA in Plasma

| PK Parameter of DHA | 120 mg dose of DHA (3 x 40 mg of DHA) |
|--|--|
| Geometric Mean (CV%) | |
| AUC _{0-t} (ng·h/mL) | 1816 (39.3%) |
| AUC _{inf} (ng·h/mL) | 1857 (39.5%) |
| C _{max} (ng/mL) | 690.5 (43.0%) |
| Arithmetic Mean (±SD) | |
| AUC _{0-t} /AUC _{inf} (%) | 96.92 (±2.541) |
| t _{1/2} (h) | 1.04 (±0.238) |
| CL/F (L/h/kg) | 1.34 (±0.473) |
| V _{area} /F (L/kg) | 2.08 (±1.08) |
| Median (Min - Max) | |
| t _{max} (h) | 2.00 (0.75 – 6.00) |

The CV% estimates for PQ were high (C_{max} PQ 61.6% and AUC₀₋₂₄ 47.0%), probably because there were multiple peaks observed for many individuals.

Table 5: Pharmacokinetic Results for PQ in Plasma

| PK Parameter of PQ | 960 mg dose of PQP (3 x 320 mg of PQP) |
|-------------------------------|---|
| Geometric Mean (CV%) | |
| AUC ₀₋₂₄ (ng·h/mL) | 1482 (47.0%) |
| C _{max} (ng/mL) | 148 (61.6%) |
| Median (Min - Max) | |
| t _{max} (h) | 4.00 (2.00 – 16.0) |

The data from these 25 adult malaria patients were included in PK compartmental analyses with separate modelling for the two actives.

- PK DHA was best described in a one-compartment model with first-order elimination and three first-order absorption processes with different absorption rate constants. Many patients exhibited multiple peaks in plasma concentration-time profiles, most likely to be due to intra-patient variability in DHA absorption from the gastrointestinal tract. It was estimated that about 28% of the bioavailable dose was absorbed with an absorption half-life of 0.617 hours. DHA exhibited “flip-flop” kinetics and this was considered to explain a mean non-compartmental t_{1/2} of 1.04 hours whereas the mean elimination half-life determined from the model was 0.448 h.
- PQ PK was best described by a three-compartment model with first-order elimination and two first-order absorption processes. The model indicated that the relative bioavailability of PQ on D1 was

87.4% compared to D0, while that on D2 was 121% of the D0 value. During the first 12 h many patients exhibited multiple peaks (or distinct phases) that suggested enterohepatic recirculation or variations in absorption through various segments of the gastrointestinal tract. The mean apparent total clearance (CL/F) was 1.12 L/h/kg. The total volume of distribution comprised a small central volume (26.7 L/kg), an intermediately sized peripheral space (76.8 L/kg) and a very large (second) peripheral space of 617 L/kg. The between patient variability was relatively high with an apparent total clearance coefficient of variability of 53% and individual estimates ranging from 0.192 to 2.68 L/h/kg. The total volume of distribution was a little less variable with a coefficient of variation of 37.5% and individual estimates ranging from 254 to 1238 L/kg. The terminal elimination half life was very long at 576 hours (24 days) as a consequence of the very extensive distribution of PQ.

The study in children with *P. falciparum* malaria (**DM04-008**) was conducted in Burkina Faso during 2006. Dosing was as shown in the table with whole or crushed tablets administered with/in 120 mL of water.

Table 6: DHA/PQP Dosing Regimen

| Weight (kg) | Total dose of DHA/day (mg) | DHA dose mg/kg/day | Total dose of PQP/day (mg) | PQP dose mg/kg/day | No. Tablets/Day |
|-------------|----------------------------|--------------------|----------------------------|--------------------|-----------------|
| 4 – 6 | 10 | 1.67 – 2.5 | 80 | 13.3 – 20 | ½ |
| 7 – 12 | 20 | 1.67 – 2.86 | 160 | 13.3 – 22.88 | 1 |
| 13 – 23 | 40 | 1.74 – 3.08 | 320 | 13.92 – 24.64 | 2 |

DHA again showed multiple-peak phenomena due to three absorption processes with slow and fast absorption rate constants varying from 0.76 to 6.20 l/h. The total (apparent) volume of distribution of DHA was 0.705 L/kg and the apparent total clearance (CL/F) was approximately 1.45 L/h/kg. The mean elimination half-life of DHA was 0.36 hours, although in many subjects flip-flop pharmacokinetics was occurring.

PQ also exhibited multiple-peak phenomena. The first absorption process involved 67% of the PQ dose, the second had a lag time of 3.8 h and occurred with a rate constant of approximately 199 L/h. The total Vss/F was very large (623 L/kg) compared to the Vc/F (27 L/kg), suggesting extensive distribution in peripheral tissues. The mean elimination half-life was about 23 days and the apparent total clearance (CL/F) was approximately 1.3 L/h/kg. The relative bioavailability for D1 was slightly lower than for D0 with a geometric mean of 95.1%, which was ascribed to inter-occasion variability. The relative bioavailability for D2 compared to D0 was higher with a geometric mean of 119%.

Due to sparse blood sampling a non compartmental analysis was not performed for DHA and PQ. As a consequence individual AUC_{INF} values were calculated as Dose/CL/F from the estimated Bayesian parameters. The correlations between CL/F or AUC_{INF} versus BW or age were estimated and positive correlations were demonstrated between DHA and PQ CL/F with BW (Pearson correlation coefficient=0.703 for DHA and =0.691 for PQ, p-values <0.001 for both). CL/F of these drugs increased as the BW increased at least in the range about 7 to 18 kg. The CL/F correlation with age was considered likely to reflect the correlation between age and BW. Conversely, no correlations were observed between AUC_{INF} values for DHA or PQ vs. BW or age, indicating comparable DHA and PQ in children who took 1 or 2 tablets of Eurartesim. From these analyses the applicant considered that the BW correction of the dose adopted for the paediatric population was justified from a pharmacokinetic point of view.

The comparison of Asian adults versus African children showed that in children the CL/F and Vss/F for PQ were within 20% of the adult values. The large volume of distribution of PQ led to very long half-life values (medians were 531 h and 468 h in adults and children, respectively). The apparent clearance was faster and the apparent total volume of distribution was smaller for the paediatric population, although the applicant considers that the differences (<20%) were not clinically important.

Table 7: Bayesian PK Parameters: PQ in The Adult And Paediatric Populations

| PQ Parameter (Unit)* | †Asian adult patients | ‡African paediatric patients |
|---|-----------------------|------------------------------|
| Apparent Clearance CL/F (L/h/kg) | 1.14 (53.0%) | 1.30 (19.0%) |
| Apparent volume of distribution V _{ss} /F (L/kg) | 730 (37.5%) | 623 (35.6%) |
| Half-life for elimination process (h) | 531 (252-4357) | 468 (84.1-3251) |

*Arithmetic means (CV%) are reported except for PQ elimination half-life, where median values (range) are reported.

Relatively small differences were observed for DHA PK between paediatric and adult populations. The mean CL/F was slightly higher while the mean Vss/F was smaller for children versus adults and the elimination rate constant was slightly faster. Again, the applicant concluded the differences were minor.

Table 8: Bayesian PK Parameters: DHA In The Adult And Paediatric Populations

| DHA Parameter (Unit)* | †Asian adult patients | ‡African paediatric patients |
|---|-----------------------|------------------------------|
| Half-life for elimination process (h) | 0.448 (41.7%) | 0.363 (37.0%) |
| Apparent Clearance CL/F (L/h/kg) | 1.340 (34.4%) | 1.450 (23.6%) |
| Apparent volume of distribution V _{ss} /F (L/kg) | 0.801 (35.5%) | 0.705 (17.3%) |

*Arithmetic means (CV%) are reported

During the assessment period the applicant provided additional PK data from three sponsored studies that had been initiated since submitting the licensing application.

These were as follows:

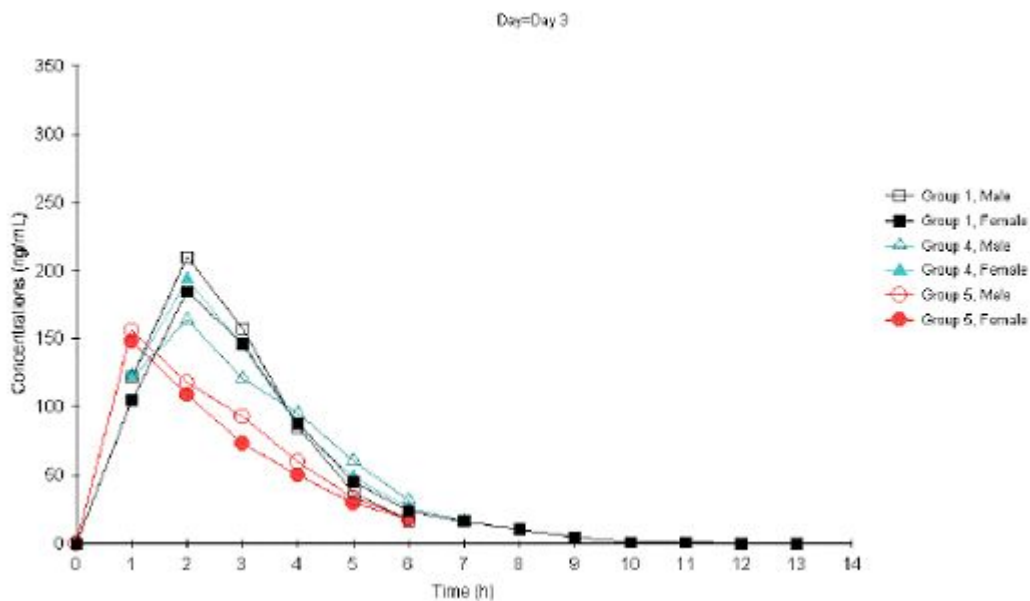
DM09-006

PK data were obtained during this parallel group study of effects on QTc vs. Riamet (artemeter/lumefantrine)(Group 2) and vs. placebo (Group 3) in healthy male and female subjects. In the four initial study groups Eurartesim was administered daily for 3 days after high fat/low kcal (Group 1) or high fat/high kcal (Group 4) meals. Two additional groups provided data on dosing in the fasted state (Group 5) vs. placebo Group 6). The study design and findings are reported under "Pharmacodynamics" (see below) along with the correlations between plasma levels and effects on QTc.

While the plasma profiles for DHA were comparable between Groups 1 and 4 (Eurartesim in the two fed states) there were some differences vs. Group 5 (fasted). There were no clear gender differences.

After repeated oral administration of Eurartesim over 3 days there was no accumulation of DHA in plasma with ratios (Day 3 / Day 1) of about 0.98 and 0.96 for C_{max} and AUC_{0-t}, respectively, in Group 1. Similarly, Group 4 data gave ratios (Day 3 / Day 1) of about 1.02 for C_{max} and 1.03 for AUC_{0-t} and the ratios for Group 5 (fasted) were 0.87 for C_{max} and 0.91 for AUC_{0-t}.

Figure 3: Mean plasma concentration of DHA vs. time profiles obtained on Day 3 after repeated oral administration of Eurartesim™ in male and female volunteers for group 1, group 4 and group 5 (linear scale)



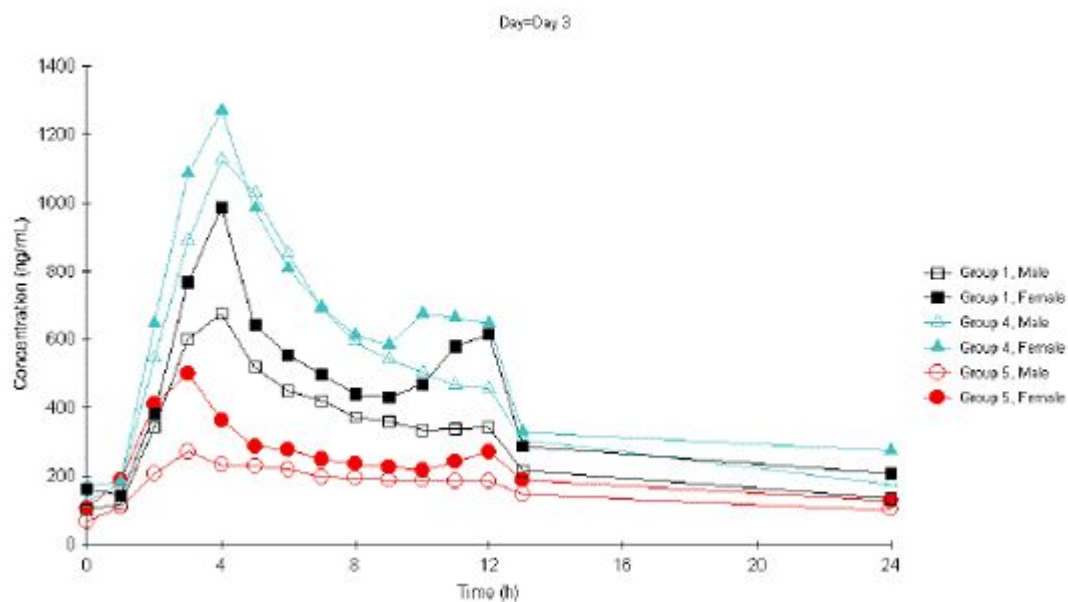
On

Day 3 there were no significant differences observed between the two groups dosed in the fed state for mean C_{max} and AUC values. However, the Day 3 comparison of the fed and fasted Groups 1 vs. 5 gave a statistically significant ($p < 0.05$) increase of about 40% in mean DHA C_{max} in the fed state. Similarly dosing with food gave an average difference of about 35% or 30% for AUC_{0-t} and AUC_{0-∞}, respectively, compared with dosing in the fasted state ($p < 0.05$). Therefore the study demonstrated a negative effect on plasma exposure to DHA when Eurartesim was dosed in the fasted state.

Mean PQ plasma profiles on Days 1 and 3 obtained in the fed state (Groups 1 and 4) followed a comparable pattern. PQ was quite slowly absorbed with a median T_{max} at 4 h post-dose in the fed state and 3 h in the fasted state. Multiple peaks were seen in the concentration-time profiles, suggesting enterohepatic recycling. After repeated dosing and regardless of fed/fasted states mean plasma PQ tended to be higher in female subjects. Repeated oral administration of Eurartesim over 3 days resulted in an increase in PQ plasma concentrations irrespective of the dosing conditions so that ratios for mean C_{max} (Day 3/Day 1) were 2.43-, 2.46- and 3.03- fold higher on Day 3 for Groups 1, 4 and 5, respectively. The same evaluation cannot be made for AUC_{0-t} because of the different sampling schemes on Days 1 and 3.

On Day 3 the mean C_{max} was 34% lower and mean AUC was 35% lower with a high-fat/low-Kcal (Group 1) than high-fat/high-Kcal (Group 4) meal ($p < 0.05$). Comparison between Groups 1 and 5 (fasted) showed that mean C_{max} was doubled when dosing was with food and there were increases of about 46% and 77% for AUC_{0-t} and AUC₀₋₂₄.

Figure 4: Mean plasma concentration of PQ vs. time profiles obtained on Day 3 after repeated oral administration of Eurartesim™ in male and female volunteers for group1, group 4 and group 5 over the first 24 h post-dose (linear scale)



DM09-007

The study directly compared PK between healthy Asian (A) and Caucasian (C) subjects of both genders and ≤ 65 kg dosed with Eurartesim (3 days) at 15 minutes after the start of a meal (360 kcal; 25% kcal from fat) and with 200 ml water.

Mean DHA AUC values on D0 (table) and on D2 (figure) were numerically higher for Asians (A). There were numerically higher exposures in female subjects. Statistically significant differences were found for T_{max} on D0, $t_{1/2}$ on D0 and D2 and AUC and CL/F on D2, giving a slightly shorter $t_{1/2}$ and higher CL/F in male subjects. The applicant proposed that the differences could be related to greater metabolic induction in male subjects since there was a more substantial decrease in AUC by D2 compared to female subjects.

Figure 5: Mean Dihydroartemisinin Concentration Profiles, Day 2 – by Ethnicity and Gender

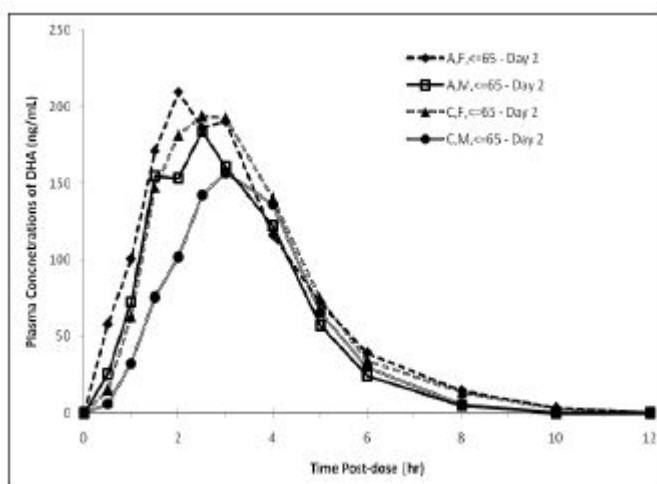


Table 9: Mean (CV%) by Ethnicity, Gender and Body Weight for Pharmacokinetic Parameters of Dihydroartemisinin – Day 0

| Group | t_{max} (hr) | C_{max} (ng/mL) | AUC_{0-12} (hr*ng/mL) | AUC_{0-last} (hr*ng/mL) | λ_z (1/hr) | $t_{1/2}$ (hr) | $AUC_{0-\infty}$ (hr*ng/mL) | V_z/F (mL) | CL/F (mL/hr) |
|---|-------------------|----------------------|----------------------------|------------------------------|-----------------------|-------------------|--------------------------------|-----------------|-------------------|
| A,F,<=65 (n=12) | 2.08 (48%) | 290 (23%) | 848 (30%) | 832 (30%) | 0.47 (29%) | 1.62 (37%) | 870 (30%) | 337742 (36%) | 149377 (29%) |
| A,M,<=65 (n=12)* | 2.46 (36%) | 267 (46%) | 762 (44%) | 740 (45%) | 0.657 (20%) | 1.09 (19%) | 800 (45%) | 272638 (44%) | 175670 (41%) |
| C,F,<=65 (n=12) | 2.5 (55%) | 248 (46%) | 742 (45%) | 728 (46%) | 0.569 (26%) | 1.30 (26%) | 756 (44%) | 377063 (70%) | 226270 (95%) |
| C,M,<=65 (n=12) | 2.71 (27%) | 216 (29%) | 662 (27%) | 643 (28%) | 0.700 (20%) | 1.03 (21%) | 671 (27%) | 280762 (30%) | 191216 (27%) |
| C,M,> 65 (n=24)* | 2.19 (40%) | 219 (50%) | 615 (37%) | 597 (38%) | 0.724 (22%) | 1.01 (25%) | 640 (34%) | 350247 (25%) | 249883 (27%) |
| Primary comparison for ethnicity | | | | | | | | | |
| A,M+F<=65 (n=24)* | 2.27 (42%) | 278 (35%) | 805 (37%) | 786 (37%) | 0.555 (29%) | 1.38 (39%) | 838 (36%) | 308149 (40%) | 161328 (36%) |
| C,M+F<=65 (n=24) | 2.61 (41%) | 232 (39%) | 702 (38%) | 686 (39%) | 0.634 (25%) | 1.16 (26%) | 714 (38%) | 328912 (60%) | 208743 (73%) |
| Secondary comparison for gender | | | | | | | | | |
| A+C,M<=65 (n=24)* | 2.58 (31%) | 241 (41%) | 712 (38%) | 692 (39%) | 0.680 (20%) | 1.06 (20%) | 730 (38%) | 277069 (36%) | 184149 (33%) |
| A+C,F<=65 (n=24) | 2.29 (52%) | 269 (35%) | 795 (37%) | 780 (38%) | 0.520 (29%) | 1.46 (35%) | 813 (37%) | 357402 (56%) | 187824 (83%) |
| Secondary comparison for body weight | | | | | | | | | |
| C,M,> 65 (n=24)* | 2.19 (40%) | 219 (50%) | 615 (37%) | 597 (38%) | 0.724 (22%) | 1.01 (25%) | 640 (34%) | 350247 (25%) | 249883 (27%) |
| C,M+F<=65 (n=24)* | 2.61 (41%) | 232 (39%) | 702 (38%) | 686 (39%) | 0.634 (25%) | 1.16 (26%) | 714 (38%) | 328912 (60%) | 208743 (73%) |

* n=10 (A,M,<=65) ; n=22 (C,M,>65; A,M+F<=65 and A+C,M<=65) for λ_z , $t_{1/2}$, $AUC_{0-\infty}$, V_z/F , CL/F

The PQ data showed no significant differences in PK according to ethnicity but CV% tended to be greater among the Caucasians. PQ did not show consistently higher AUCs in female subjects but there was a statistically significantly higher C_{max} in females on D2 with a longer $t_{1/2}$.

Figure 6: Mean Piperazine Concentration Profiles, Day 2 – by Ethnicity and Gender

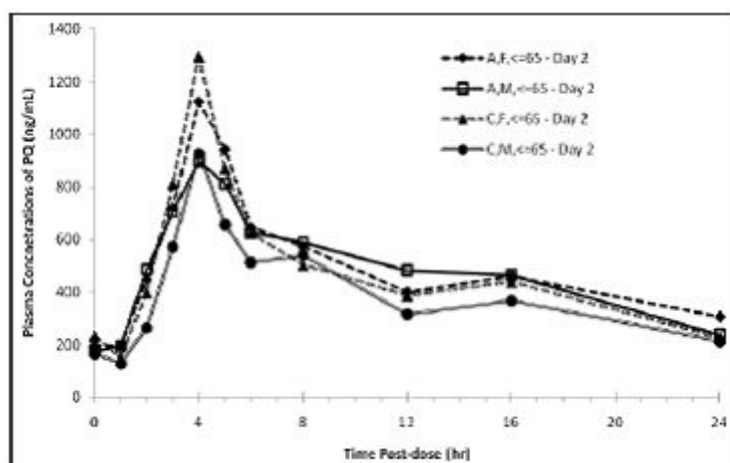


Table 10 Mean (CV%) by Ethnicity, Gender and Body Weight for Pharmacokinetic Parameters of Piperazine – Day 0

| Group | t_{max} (hr) | C_{max} (ng/mL) | AUC_{0-24} (hr*ng/mL) |
|---|-------------------|----------------------|----------------------------|
| A,M,<=65 (n=11) | 3.73 (21%) | 579 (21%) | 4796 (12%) |
| A,F,<=65 (n=12) | 4.17 (23%) | 472 (38%) | 3776 (36%) |
| C,M,<=65 (n=11) | 4.19 (21%) | 396 (34%) | 3141 (24%) |
| C,F,<=65 (n=11) | 3.91 (21%) | 632 (49%) | 4240 (44%) |
| C,M,> 65 (n=21) | 3.76 (24%) | 535 (56%) | 3884 (43%) |
| Primary comparison for ethnicity | | | |
| C,M+F,<=65 (n=22) | 4.05 (21%) | 514 (51%) | 3690 (40%) |
| A,M+F,<=65 (n=23) | 3.96 (22%) | 523 (31%) | 4264 (27%) |
| Secondary comparison for gender | | | |
| C+A,M,<=65 (n=22) | 3.96 (21%) | 487 (32%) | 3968 (27%) |
| C+A,F,<=65 (n=23) | 4.04 (22%) | 549 (47%) | 3998 (40%) |
| Secondary comparison for body weight | | | |
| C,M,> 65 (n=21) | 3.76 (24%) | 535 (56%) | 3884 (43%) |
| C,M+F,<=65 (n=22) | 4.05 (21%) | 514 (51%) | 3690 (40%) |

Table 11: Mean (CV%) by Ethnicity, Gender and Body Weight for Pharmacokinetic Parameters of Piperaquine – Day 2

| Group | t_{\max} (hr) | C_{\max} (ng/mL) | AUC_{0-24} (hr*ng/mL) | $AUC_{0-\text{last}}$ (hr*ng/mL) | Day2/Day0 AUC_{0-24} (%) |
|---|--------------------|-----------------------|----------------------------|-------------------------------------|-------------------------------|
| A,M,<=65 (n=11) | 4.09 (17%) | 1057 (29%) | 11581 (18%) | 52954 (22%) | 2.4 (10%) |
| A,F,<=65 (n=12) | 4.42 (15%) | 1238 (34%) | 11856 (26%) | 47457 (32%) | 3.4 (27%) |
| C,M,<=65 (n=11) | 4.18 (10%) | 944 (41%) | 9350 (34%) | 40038 (31%) | 3.0 (19%) |
| C,F,<=65 (n=11) | 4.45 (29%) | 1367 (39%) | 11180 (26%) | 47520 (31%) | 4.0 (119%) |
| C,M,> 65 (n=21) | 3.95 (28%) | 862 (40%) | 9169 (29%) | 40624 (22%) | 2.6 (26%) |
| Primary comparison for ethnicity | | | | | |
| C,M+F,<=65 (n=22) | 4.32 (22%) | 1155 (43%) | 10265 (30%) | 43779 (32%) | 3.5 (96%) |
| A,M+F,<=65 (n=23) | 4.26 (16%) | 1152 (32%) | 11724 (22%) | 50086 (27%) | 2.9 (29%) |
| Secondary comparison for gender | | | | | |
| C+A,M,<=6 (n=22) | 4.14 (14%) | 1001 (34%) | 10465 (27%) | 46496 (29%) | 2.7 (19%) |
| C+A,F,<=65 (n=23) | 4.43 (22%) | 1300 (36%) | 11533 (26%) | 47487 (31%) | 3.6 (89%) |
| Secondary comparison for body weight | | | | | |
| C,M,> 65 (n=21) | 3.95 (28%) | 862 (40%) | 9169 (29%) | 40624 (22%) | 2.6 (26%) |
| C,M+F,<=65 (n=22) | 4.32 (22%) | 1155 (43%) | 10265 (30%) | 43779 (32%) | 3.5 (96%) |

In overall comparisons between subjects grouped by ethnicity, gender, body weight range and dose level, the only differences in PK found to be statistically significant were:

For PQ in female subjects

- higher C_{\max} for PQ in female subjects on D2

For DHA in female subjects

- lower T_{\max} at D0
- longer half-life on D0 and D2
- higher AUC on D2 with corresponding lower CL/F

An additional cohort of 24 male Caucasians of body weight > 65 kg was enrolled and received 3 or 4 tablets daily (with the same light breakfast) according to weight \leq or > 75 kg. The Caucasian male and female subjects with BW \leq 65 kg had numerically higher plasma exposures to DHA and PQ on D0 and D2 vs. the additional cohort of Caucasian male subjects with BW > 65 kg.

Table 12: Mean (CV%) by BW for pharmacokinetic parameters of DHA – Day 2

| Group | t_{\max}^* (hr) | C_{\max} (ng/mL) | AUC_{0-12} (hr*ng/mL) | $AUC_{0-\text{last}}$ (hr*ng/mL) | λ_z (1/hr) | $t_{1/2}$ (hr) | $AUC_{0-\infty}$ (hr*ng/mL) | V_z/F (L) | CL/F (L/hr) |
|---------------------|----------------------|-----------------------|----------------------------|-------------------------------------|-----------------------|-------------------|--------------------------------|----------------|------------------|
| C,M+F<=65 (n=24) | 3.0 (1.5-4) | 266 (46) | 649 (36) | 634 (36) | 0.651 (27) | 1.15 (29) | 674 (36) | 308 (21) | 199 (34) |
| C,M,>65 (n=24) | 2.0 (1-4) | 210 (44) | 563 (35) | 545 (36) | 0.692 (27) | 1.12 (45) | 595 (35) | 444 (50) | 283 (37) |

* Median (range)

Table 13: Mean (CV%) by BW for pharmacokinetic parameters of PQ – Day 0 and 2

| Group | Day 0 | | | Day 2 | | | | Day2/Day0 AUC ₀₋₂₄ (%) |
|--------------------------------|---------------------------------------|-----------------------------|-----------------------------------|--------------------------|-----------------------------|-----------------------------------|-------------------------------------|--------------------------------------|
| | t _{max} [*] (hr) | C _{max} (ng/mL) | AUC ₀₋₂₄ (hr*ng/mL) | t _{max} (hr) | C _{max} (ng/mL) | AUC ₀₋₂₄ (hr*ng/mL) | AUC _{0-last} (hr*ng/mL) | |
| C,M+F≤65 (n=20) | 4.0 (3-6) | 504 (54) | 3583 (42) | 4.0 (3-8) | 1157 (45) | 10265 (31) | 36969 (27) | 3.6 (96) |
| C,M ₁ >65 (n=20) | 4.0 (3-6) | 542 (56) | 4105 (39) | 4.0 (2-8) | 881 (39) | 9308 (29) | 33576 (19) | 2.6 (27) |

* Median (range)

The comparison between mixed gender groups that received 3 tablets/day and the male subjects who received 4 tablets/ day showed no appreciable difference in AUCs on D0 or D2 for DHA. There was also no difference between dose groups for AUCs on D2 for PQ although higher mean C_{max} and AUC were observed with 4 tablets on D0.

Table 14: Mean (CV%) pharmacokinetic parameters of DHA – D2

| Group | t _{max} [*] (hr) | C _{max} (ng/mL) | AUC ₀₋₁₂ (hr*ng/mL) | AUC _{0-last} (hr*ng/mL) | λ _z (1/hr) | t _{1/2} (hr) | AUC _{0-∞} (hr*ng/mL) | V _z /F (L) | CL/F (L/hr) |
|---------------------------|---------------------------------------|-----------------------------|-----------------------------------|-------------------------------------|--------------------------|--------------------------|----------------------------------|--------------------------|----------------|
| C,M+F,3 tablets (n=31) | 3.0 (1.5-4) | 216 (46) | 612 (37) | 596 (38) | 0.675 (26) | 1.11 (30) | 646 (36) | 310 (22) | 208 (34) |
| C,M+4, tablets (n=17) | 2.0 (1-4) | 223 (43) | 595 (35) | 576 (36) | 0.665 (30) | 1.19 (47) | 616 (36) | 484 (49) | 295 (39) |

Table 15: Mean (CV%) pharmacokinetic parameters of PQ – D0 and 2

| Group | Day 0 | | | Day 2 | | | | Day2/Day0 AUC ₀₋₂₄ (%) |
|---------------------------|---------------------------------------|-----------------------------|-----------------------------------|---------------------------------------|-----------------------------|-----------------------------------|-------------------------------------|---|
| | t _{max} [*] (hr) | C _{max} (ng/mL) | AUC ₀₋₂₄ (hr*ng/mL) | t _{max} [*] (hr) | C _{max} (ng/mL) | AUC ₀₋₂₄ (hr*ng/mL) | AUC _{0-last} (hr*ng/mL) | |
| C,M+F,3 tablets (n=24) | 4.0 (3-6) | 461 (59%) | 3455 (43%) | 4.0 (2-8) | 1074 (48%) | 9742 (33%) | 35568 (28%) | 3.6 (89%) |
| C,M+4, tablets (n=16) | 4.0 (3-5) | 616 (47%) | 4387 (34%) | 4.0 (3-8) | 936 (36%) | 9855 (25%) | 34828 (16%) | 2.4 (20%) |

To further explore the proposed dose adjustment by body weight at the 75 kg cut-off the applicant provided plots based on corresponding PK parameters vs. BW from DM09-006, 007 and 008 (see below).

- DHA CL/F but not V_z/F positively correlated (p < 0.0001) with BW up to 75 kg. In the BW range 75 to ~100 kg the CL/F seemed to be constant, which the applicant considers to be an indication that a further dose adjustment for BW is not necessary.
- For PQ mean C_{max} and AUC₀₋₂₄ after a single dose of drug were compared to BW due to the different dose regimens, blood sampling schemes and the PQ half-life. Also, subjects who received Eurartesim without food (DM09008) were excluded from the plots so the analysis concerned only subjects dosed with a light meal or a high fat meal. The plots indicate that C_{max} and AUC values were very variable but the spread of values was comparable regardless of whether subjects received 3 or 4 tablets according to body weight.

DM09-008

This was a food effect study in healthy Caucasian male subjects ≥ 75 kg. Subjects were randomised to one of two parallel groups to take a single dose of Eurartesim (4 tablets; 160 mg DHA and 1280 mg PQP) as follows:

- Fed treatment: 4 tablets Eurartesim™ with 200 mL water, following a standardised high fat and high calorie breakfast, starting 30 minutes prior to dose administration.
- Fasted treatment: 4 tablets Eurartesim™ with 240 mL water, following an overnight fast of at least 10 hours

The high fat meal provided 800-1000 kcal with 500-600 kcal derived from the fat content. No food and only water was allowed from 1-4 h after dosing. The two groups received tablets from different sub-lots. Blood samples were collected very frequently in the first 24 h and then at intervals to 60 h followed by daily sampling out to 7 days.

For DHA, the $AUC_{0-\infty}$ was significantly greater in the fed state (mean ratio fed/fasted = 144%) while the C_{max} ratio was 129% (not statistically significant at the 5% level). There was also a significant delay in median T_{max} from 1 to 2 h.

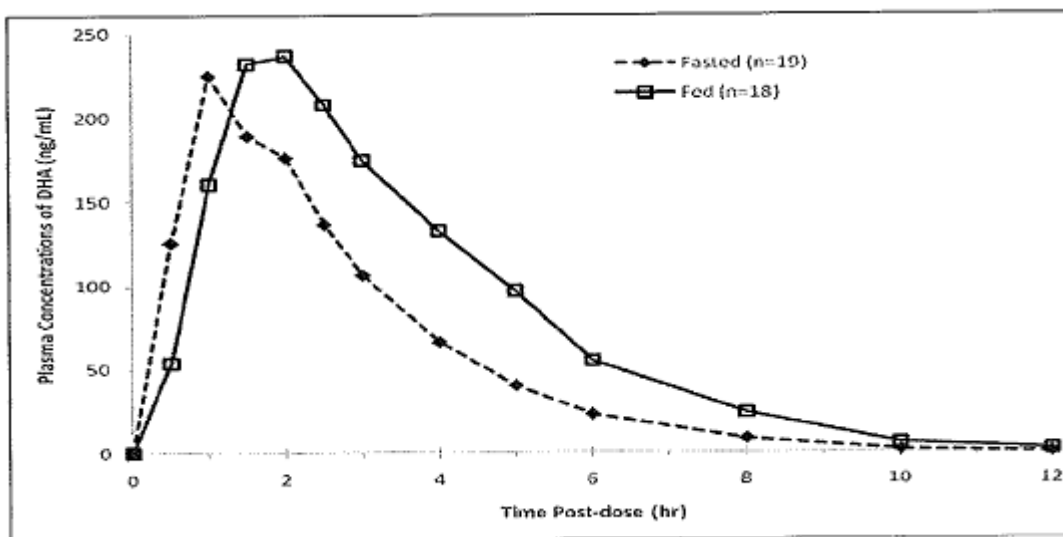
Table 16: Mean (CV%) of Pharmacokinetic Parameters of Dihydroartemisinin – by Fed/Fasted Condition

| Group | t_{max} (hr) | C_{max} (ng/mL) | AUC_{0-last} (hr*ng/mL) | λ_z (1/hr) | $t_{1/2}$ (hr) | $AUC_{0-\infty}$ (hr*ng/mL) | V_z/F (mL) | CL/F (mL/hr) |
|------------------|-------------------|----------------------|------------------------------|-----------------------|-------------------|--------------------------------|------------------|-------------------|
| Fed (n=18) | 2.47 (55%) | 324 (48%) | 933 (36%) | 0.479* (18%) | 1.49* (18%) | 1009* (30%) | 373832* (41%) | 175473* (38%) |
| Fasted (n=19) | 1.16 (39%) | 252 (42%) | 649 (37%) | 0.521 (32%) | 1.44 (27%) | 684 (36%) | 534918 (38%) | 272816 (48%) |

Reference: Table 14.3.2.3

* n=17

Figure 7: Mean Dihydroartemisinin Concentration Profiles – by Fed/Fasted



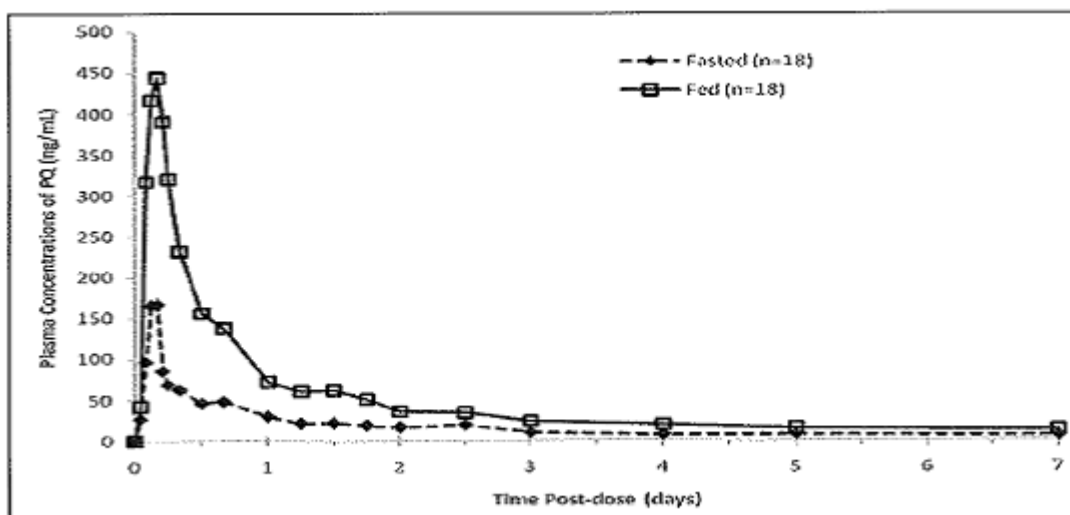
For PQ, the C_{max}, AUC₀₋₂₄ and AUC_{0-last} (T_{last} = 168 h) were all significantly higher in the fed state with mean ratios for fed/fasted of 317%, 317% and 277%, respectively. There was no difference in median T_{max} for PQ between the fed and fasted groups.

Table 17: Mean (CV%) of Pharmacokinetic Parameters of Piperaquine – by Fed/Fasted Condition

| Group | t _{max} (hr) | C _{max} (ng/mL) | AUC ₀₋₂₄ (hr*ng/mL) | AUC _{0-last} (hr*ng/mL) |
|------------------|--------------------------|-----------------------------|-----------------------------------|-------------------------------------|
| Fed (n=18) | 3.83 (34%) | 596 (34%) | 4537 (23%) | 8333 (21%) |
| Fasted (n=18) | 3.39 (25%) | 188 (75%) | 1431 (53%) | 3010 (47%) |

Reference: Table 14.3.2.4

Figure 8: Mean Piperaquine Concentration Profiles to 7 Days Post-dose – by Fed/Fasted



From comparisons across sponsored studies (see tables below) the data suggested that plasma exposures to DHA are greater in infected subjects vs. healthy volunteers whereas for PQ the effect of acute malaria on plasma exposures was concluded to be minimal or negligible.

For DHA there is an effect of food. However there is overlap in values reported among the various groups of healthy subjects dosed in fed and fasted states and a stark difference between all these values and those for the subjects with acute malaria from whom PK data were obtained in the Phase 2 study DM04-009. This is especially notable when taking into account that the applicant claimed they were likely dosed at least 3-6 h after any food intake.

For PQ the picture is quite different since the effect of food is much greater and this predominates over the comparisons made, assuming that the low plasma exposures in Asians with malaria reflects the fact that they were likely dosed on an empty or near empty stomach. The applicant considers that dosing PQ in the fasted state was associated with a higher degree of inter-subject variability for PK parameters than in fed subjects as shown in Table 113.2, which is proposed to reflect the lower and more variable PQQ absorption in the absence of concomitant food intake.

Table 18: DHA CV% of C_{max} and AUC_{INF} in sigma-tau studies in Healthy Volunteers and Patients Ethnicity, Gender, Body Weight (Dose) and Dietary Intake

| Study code | Subjects | Origin | Gender | No. of Subjects | DHA dose (mg) (tablets) | Food Intake | PK Modelling | Mean (CV%) Day 1 C_{max} (ng/mL) | Mean (CV%) Day 1 $AUC_{0-\infty}$ (ng/mL.h) |
|------------------------|----------|-----------|-----------|-----------------|-------------------------|--------------|--------------|------------------------------------|---|
| ART-DFM-05-002 | HV | Caucasian | Male<75kg | 16 | 40 (1) | Fasted | NCA | 38.9 (88%) | 98.1 (50%) |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 9 | 161 (4) | Fasted | NCA | 166 (37%) ^a | 510 (35%) ^a |
| ST3073-ST3074 D0409008 | HV | Caucasian | Male<75kg | 19 | 160 (4) | Fasted | NCA | 252 (42%) | 684 (36%) |
| ST3073-ST3074 D0409008 | HV | Caucasian | Male<75kg | 18 | 160 (4) | 800-1000kcal | NCA | 324 (48%) | 1009 (30%) |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 14 | 160 (4) | ca. 963kcal | NCA | 235 (45%) ^a | 696 (40%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 14 | 160 (4) | ca. 347kcal | NCA | 277 (35%) ^a | 756 (31%) ^a |
| ST3073-ST3074 D0409007 | HV | Caucasian | Male<75kg | 17 | 160 (4) | ca. 359kcal | NCA | 223 (43%) | 616 (36%) |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 15 | 120 (3) | Fasted | NCA | 189 (40%) ^a | 520 (34%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 11 | 120 (3) | ca. 963kcal | NCA | 295 (41%) ^a | 580 (21%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 26 | 120 (3) | ca. 347kcal | NCA | 236 (43%) ^a | 604 (35%) ^a |
| ST3073-ST3074 D0409007 | HV | Caucasian | Male<75kg | 19 | 120 (3) | ca. 359kcal | NCA | 209 (44%) | 619 (32%) |
| ST3073-ST3074 D0409006 | HV | Caucasian | Female | 16 | 120 (3) | Fasted | NCA | 161 (44%) ^a | 478 (38%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Female | 15 | 120 (3) | ca. 963kcal | NCA | 229 (36%) ^a | 675 (31%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Female | 24 | 120 (3) | ca. 347kcal | NCA | 227 (37%) ^a | 650 (33%) ^a |
| ST3073-ST3074 D0409007 | HV | Caucasian | Female | 12 | 120 (3) | ca. 359kcal | NCA | 248 (46%) | 756 (44%) |
| ST3073-ST3074 D0409007 | HV | Asian | Female | 12 | 120 (3) | ca. 359kcal | NCA | 290 (23%) | 870 (30%) |
| ST3073-ST3074 D0409007 | HV | Asian | Male<75kg | 12 | 120 (3) | ca. 359kcal | NCA | 267 (46%) | 800 (45%) |
| ST3073-ST3074 D0404009 | Patients | Asian | Male<75kg | 25 | 120 (3) | A | NCA | 752 (47%) | 2002 (45%) |

A: Patients were not fasted before dosing, the recorded fasting period was in the range of 3 to 6 h pre-dose, (median 4.5); NCA: Non compartmental Analysis; HV: Healthy volunteers; NA: not available; a) observed on last day of treatment assumed as not different from those of Day 1.

Table 19: PQ (CV%) of C_{max} and AUC_{0-24} in sigma-tau studies in Healthy Volunteers and Patients by Ethnicity, Gender, Body Weight (Dose) and Dietary Intake

| Study code | Subjects | Origin | Gender | No. of Subjects | PQ dose (mg) (tablet) | Food Intake | PK Modelling | Mean (CV%) Day 1 C_{max} (ng/mL) | Mean (CV%) Day 1 AUC_{0-24} (ng/mL.h) |
|------------------------|----------|-----------|-----------|-----------------|-----------------------|--------------|--------------|------------------------------------|---|
| ART-DFM-05-002 | HV | Caucasian | Male<75kg | 16 | 320 (1) | Fasted | NCA | 24 (34%) | N/A |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 9 | 1280 (4) | Fasted | NCA | 117 (55%) ^a | 1415 (35%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 18 | 1280 (4) | Fasted | NCA | 188 (75%) ^a | 1437 (53%) |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 18 | 1280 (4) | 800-1000kcal | NCA | 596 (34%) | 4531 (23%) |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 14 | 1280 (4) | ca. 963kcal | NCA | 463 (36%) ^a | 4121 (30%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 14 | 1280 (4) | ca. 347kcal | NCA | 307 (35%) ^a | 2838 (39%) ^a |
| ST3073-ST3074 D0409007 | HV | Caucasian | Male<75kg | 16 | 1280 (4) | ca. 359kcal | NCA | 616 (47%) | 4387 (34%) |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 15 | 960 (3) | Fasted | NCA | 114 (35%) ^a | 1401 (30%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 11 | 960 (3) | ca. 963kcal | NCA | 418 (30%) ^a | 3663 (29%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Male<75kg | 26 | 960 (3) | ca. 347kcal | NCA | 248 (32%) ^a | 2378 (25%) ^a |
| ST3073-ST3074 D0409007 | HV | Caucasian | Male<75kg | 16 | 960 (3) | ca. 359kcal | NCA | 358 (41%) | 2871 (32%) |
| ST3073-ST3074 D0409006 | HV | Caucasian | Female | 16 | 960 (3) | Fasted | NCA | 211 (50%) ^a | 1947 (35%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Female | 15 | 960 (3) | ca. 963kcal | NCA | 498 (28%) ^a | 4533 (35%) ^a |
| ST3073-ST3074 D0409006 | HV | Caucasian | Female | 24 | 960 (3) | ca. 347kcal | NCA | 373 (40%) ^a | 3448 (36%) ^a |
| ST3073-ST3074 D0409007 | HV | Caucasian | Female | 11 | 960 (3) | ca. 359kcal | NCA | 632 (49%) | 4240 (44%) |
| ST3073-ST3074 D0409007 | HV | Asian | Female | 12 | 960 (3) | ca. 359kcal | NCA | 472 (38%) | 3776 (36%) |
| ST3073-ST3074 D0409007 | HV | Asian | Male<75kg | 11 | 960 (3) | ca. 359kcal | NCA | 579 (21%) | 4796 (12%) |
| ST3073-ST3074 D0404009 | Patients | Asian | Male<75kg | 25 | 960 (3) | A | NCA | 179 (62%) | 1679 (47%) |

A: Patients were not fasted before dosing, the recorded fasting period was in the range of 3 to 6 h pre-dose, (median 4.5); NCA: Non compartmental Analysis; HV: Healthy volunteers; a) calculated from parameters observed on last day of treatment and divided by an accumulation index of 3 estimated from all population involved in the study DM09007 (and also corrected for analytical bias, see CSR DM09-006).

Factors that might contribute to the observed inter-subject variability include the PQ and DHA concentrations in RBCs and the large volume of distribution for PQ. The concentrations of both drugs determined in plasma represent a minor part of the total drug in circulation and inter-individual variation in blood/plasma and/or tissue/plasma partition coefficients may produce variability in plasma concentrations.

Absorption

Bioavailability

In a published study single oral doses of artesunate (3 x 50 mg tablets) and DHA (2 x 60 mg tablets) and an IV dose of 120 mg artesunate were each administered to healthy subjects and subjects with *P. falciparum* malaria in a cross-over design.

The absolute bioavailability of DHA was consistently lower after administration of DHA than after administration of oral artesunate in the healthy volunteers (45% and 80%, respectively) and was attributed to lower DHA absorption and/or a higher first-pass effect. The relative bioavailability of oral DHA compared to oral artesunate in patients was 88%. C_{max} and AUC were significantly greater in patients with malaria than in healthy volunteers. This was possibly attributed to a lower first-pass clearance. The terminal elimination half-life of DHA was about 1 h in healthy volunteers and patients.

Eurartesim tablets were administered whole or crushed in the Phase 3 studies in accordance with the protocol. The applicant demonstrated that the dissolution profiles (as assessed at pH 1.2, 4.5 and 6.8, with and without surfactant) for the crushed and un-crushed tablets were super-imposable, indicating that the DHA absorption profile should be the same in children taking either a crushed or an un-crushed tablet. The dissolution testing under similar conditions for PQP also showed no differences between crushed and un-crushed tablets. Also, since the PQ absorption process is very slow with T_{max} at about 5 h so it is unlikely that the rate of dissolution would significantly influence PQ absorption.

Distribution

The applicant's studies using a monolayer of a CLEFF9 sub-clone of human Caco-2 cells with high P-glycoprotein-mediated efflux suggested that DHA (1 and 20 µM) and PQP (20 µM) are not substrates for P-glycoprotein. Evaluation of the plasma protein binding of PQ in rat, dog and humans *in vitro* indicated that binding in all species tested could be considered virtually complete (>99% at the highest concentration tested). In another study reported by the applicant the blood to plasma ratio of PQ *in vivo* in rat was found to be around 4.4 - 7.0 up to 8 h with a ratio of 26.5 at 24 h post-dosing with 14C-PQP/DHA in combination.

The in-vitro protein binding of DHA has been reported to be in the range of 47-76%. In one study 10-[3H]-DHA was incubated with blood from 15 healthy volunteers (Vietnamese and Caucasian) and from 22 Vietnamese patients infected with *P. falciparum* or *P. vivax* previously treated with artesunate. The results suggested that DHA is approximately 93% protein bound in patients with malaria and 88-91% bound in healthy volunteers. [3H]-DHA is taken up and concentrated by isolated red blood cell membranes but not by intact uninfected erythrocytes. There is no association of the drug with either the membrane or cytoplasm of intact red cells. In addition, erythrocytes infected with *P. falciparum* have been shown to take up artemisinin derivatives to concentrations greater than 100-fold those in uninfected erythrocytes. This selective uptake has been demonstrated to involve a carrier-mediated mechanism in contrast to the simple, passive diffusion of artemisinins into non-infected red blood cells.

Elimination

Dose proportionality and time dependencies

Information was provided from the literature.

- The pharmacokinetic properties of PQ were assessed from a 2008 study in which subjects received single ascending oral doses of 500, 750, 1000, 1250 and 1500 mg PQP and also once-daily doses of 500, 750, 1000 and 1500 mg for 3 consecutive days. The dose exposure relationship was linear but less than proportional after single and multiple dosing.
- A 2004 study included 20 healthy male and female Thai subjects who received a single dose of DHA of 2 or 4 mg/kg, which corresponded to a total dose ~100 and 200 mg for a 50 kg person. Analyses conducted according to non compartmental and (one) compartmental approaches gave comparable values of dose-independent PK parameters at both doses tested. Linearity was demonstrated by dose-proportional increases in C_{max} and AUC_{INF} .

Special populations

Regarding the effects of renal and hepatic impairment on the pharmacokinetics of DHA and/or PQ:

- Malaria *per se* has an effect on DHA disposition, which may reflect malaria-associated impairment of hepatic function causing an increase in DHA bioavailability (reduction in hepatic first-pass extraction) without affecting its apparent elimination half-life, which is absorption rate limited.
- Severe malaria can also have an impact on renal function but data from a study of intravenous artesunate to treat severe and moderately severe malaria suggested that renal impairment complicating falciparum malaria did not alter DHA clearance significantly.
- It is considered unlikely that mild or moderate renal impairment would have an effect on the disposition of PQ. A slight reduction in protein binding of neutral or basic compounds could slightly increase CL/F and V_{ss}/F but it is not thought this would occur to a clinically significant extent.
- Hepatic impairment may influence PQ disposition. In cirrhotic patients, a decrease in protein binding and metabolic clearance may have an impact on PQ plasma concentrations and on its V_{ss}/F , causing also a prolongation of PQ half-life. Furthermore in case of obstructive jaundice, the excretion of PQ through the bile may be compromised.
- In the absence of clinical data in patients with severe renal or hepatic impairment and the limited experience in subjects with lesser degrees of insufficiency, the SmPC advises caution when administering Eurartesim with a specific recommendation for ECG and blood potassium monitoring. Specific studies in patients with moderate or severe renal and/or hepatic impairment are not planned by the applicant given the very low frequency with which such patients are expected to travel from Europe to malaria-endemic areas.

Regarding the potential for genetic polymorphism to affect the pharmacokinetics of DHA and/or PQ:

- PQ - There is no evidence that CYP3A4 gene polymorphism plays a major role in establishing highly variable CYP3A4 expression and function although, in very rare cases, defective CYP3A4 mutations may cause drug toxicity. A small proportion of the population (up to 6% in different ethnic groups) are CYP2C9 poor metabolisers while 2-7% of Africans, 10-30% of Asians and 2-5% of Caucasians are CYP2C19 poor metabolisers. Poor metabolisers may exhibit a several-fold higher than average area under the plasma concentration-time curve (AUC) after administration of compounds that are

exclusive substrates of CYP2C9 or CYP2C19. However, considering the low clearance of PQ and the minor contribution of CYP2C9 and CYP2C19 to its metabolism, significant differences in plasma concentrations between poor and extensive metabolisers are not expected.

- DHA - UGT2A9 and UGT2B7 are known to have genetic variants. The UGT1A9 poor metaboliser phenotype occurs in < 1% of persons but 4-10% of Africans, 6-7% of Asians and 20-25% of Caucasians are poor metabolisers for UGT2B7. Nevertheless, UGT2B7 makes only a minor contribution to DHA metabolism so it is considered unlikely that variations in enzyme activity would have a significant effect on plasma concentrations.

Pharmacokinetic interaction studies

No drug-drug interaction studies were performed. Regarding the potential for absorption-based drug-drug interactions with DHA and/or PQ:

- Published findings suggest that DHA (1 and 20µM) and PQ (20µM) are not substrates for P-gp. PQ was shown to be a weak inhibitor of P-gp so it might affect the absorption of P-gp substrates (e.g. digoxin). However, the mean IC₅₀ was 74 µM in the B-A direction and 11 mM in the A-B direction with the IC₅₀ determined from the efflux of 3H-digoxin being 7 µM.
- DHA is practically insoluble in water. Although DHA is sensitive to acidic conditions it is not expected that antacids, H₂-antagonists or proton-pump inhibitors would have an influence on absorption and it is unlikely that DHA could affect the absorption of other drugs.
- PQP is slightly soluble in water and its solubility is expected to decrease at increased pH. This raises the possibility that antacids, H₂-antagonists or proton-pump inhibitors might impact on PQ bioavailability due to reduced solubility. However, the PQ absorption process is very slow (T_{max} ~ 5 h), suggesting that significant absorption does not occur in the stomach. Therefore, medicinal products that increase gastric pH are not expected to have an effect.
- The enterohepatic recirculation of PQ and influence of food indicate that bile production may play a role in PQ absorption.

Results of the sponsor's study of the potential for PQ and DHA to inhibit and/or induce enzymes of possible metabolic importance are summarised in the table.

Table 20

| study 8740133 | PQ | | | DHA | | |
|----------------|------------------|------------------|----------------|------------------|------------------|----------------|
| | substrate | inhibitor | inducer | Substrate | inhibitor | inducer |
| CYP3A | - | yes ^a | no | - | no | no |
| CYP3A4 | yes | yes ^b | - | No | no | - |
| CYP3A5 | no | - | - | No | - | - |
| CYP2C19 | weak | yes | - | No | weak | - |
| CYP2C9 | weak | no | - | No | no | - |
| CYP2B6 | no | weak | no | No | no | no |
| CYP2C8 | no | weak | - | No | no | - |
| CYP1A | - | no | no | - | yes | no |
| CYP1A2 | no | no | - | No | yes ^d | - |
| CYP2D6 | no | no | - | No | no | - |
| CYP2E1 | no | stimulator | - | No | no | - |
| UGT1A1 | no | weak | - | No | no | - |
| UGT2B7 | - | - | - | no ^c | - | - |
| P-gp | nc | weak | - | No | no | - |

a) also time dependent

b) PQ inhibited CYP3A4 with an IC₅₀ of 5µM (Gigras R et al. 2008)

c) UGT1A9 was the main isoform for DHA metabolism, although a contribution of UGT2B7 was observed. DHA was not substrate in UGT1A1 and UGT1A6 (Ilett et al 2002).

d) Also observed by Bapiro et al. 2001

nc: the efflux ratio can not be calculated (test compound in the receiver samples was below the limit of quantitation)

PQ was mainly metabolised by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. PQ at 10µM inhibited CYP3A4 in a time-dependent fashion and CYP2C19 but stimulated the activity of CYP2E1. PQ did not induce CYP1A, CYP2B6 or CYP3A at 0.1-10 µM. The fact that PQ was not an inducer of CYP2A implies that it is also not likely to induce CYP2C8, CYP2C9 or CYP2C1. Furthermore, it is unlikely that PQ is an inducer of P-gp since the induction of both CYP3A and P-gp are regulated by PXR.

PQ has the potential to increase plasma concentrations of CYP3A4 substrates, such as HMG CoA reductase inhibitors and some drugs with a narrow therapeutic index might also be affected (e.g. anti-retroviral drugs and cyclosporin). Co-administration might lead to increases in plasma levels of several drugs that prolong the QT interval (e.g. macrolides, pimozide, terfenadine, astemizole, cisapride). PQ may reduce the rate of metabolism of CYP2C19 substrates such as omeprazole and decrease plasma concentrations of CYP2E1 substrates such as paracetamol and the anaesthetic gases (enflurane, halothane, isoflurane).

In the applicant's study DHA was not an inducer of CYP1A, CYP2B6 or CYP3A at 0.1-25µM). DHA was not an inducer of CYP2A so it is not likely to induce CYP2C8, CYP2C9, CYP2C1 or P-gp. It has been reported in the literature that DHA inhibits CYP1A2 *in vitro* while it showed a small effect *in vivo* on some cytochrome P450 isoenzymes in terms of increasing CYP3A activity by a median factor of 1.25 (midazolam as substrate) and decreasing the activity of CYP1A2 (caffeine as substrate) and CYP2D6 (metoprolol as substrate) by median factors of 0.73 and 0.83, respectively. These effects were not thought to have clinical significance but the applicant states that it is appropriate to exercise caution when administering DHA concomitantly with CYP1A2 substrates with a narrow therapeutic index (e.g. theophylline).

Regarding the possible effects of other drugs on DHA and PQ:

- PQ clearance may be reduced by concomitant use of CYP3A4 inhibitors such as NNRTIs (delavirdine, efavirenz), protease inhibitors (amprenavir, indinavir), calcium channel blockers (diltiazem), H2-receptor antagonists (cimetidine), hormonal contraceptives (gestodene, ethyloestradiol) or grapefruit juice.

- PQ clearance may be increased by CYP3A4 inducers including the NNRTI nevirapine, anticonvulsant and antiepileptic agents (carbamazepine, phenobarbital, phenytoin), antibacterial agents (rifampicin, rifabutin, rifapentine), glucocorticoids and St. John's wort. However, since the PQ half-life is >20 days and most of the drug is rapidly distributed to tissues rather than circulating in the blood an alteration in its clearance would affect mostly the terminal phase when concentrations are very low. In addition, while PQ pharmacokinetics might be affected by the listed drugs the applicant does not expect clinically relevant implications and has not proposed specific SmPC text on this topic.
- Declining concentrations of DHA and its pro-drug artesunate have been reported after multiple administrations to healthy volunteers and subjects with acute malaria but the mechanism behind self-induction is unknown. It has been reported that systemic exposure (AUC_{0-∞}) was not statistically significantly reduced over a 3-day treatment period and there is currently no evidence of impaired efficacy due to this phenomenon.
- The applicant considers it is unlikely that inhibitors of UGT1A9 would increase DHA plasma concentrations, in fact DHA is possibly metabolised also by UGT2B7. Inducers of UGT enzymes like phenobarbital might decrease DHA plasma concentrations.

2.4.3. Pharmacodynamics

Mechanism of action

The applicant did not conduct studies but quoted published data on what is known about the mechanism of action of the active substances. Details are noted in section "Primary pharmacodynamics".

Primary and Secondary pharmacology

Primary pharmacodynamics.

The endoperoxide bridge construct in the artemisinins is thought to be essential for their anti-malarial activity, causing free-radical damage to parasite membrane systems. Specific actions include:

- Inhibition of *falciparum* sarcoplasmic-endoplasmic reticulum calcium ATPase
- Interference with mitochondrial electron transport
- Interference with parasite transport proteins
- Disruption of parasite mitochondrial function.

In addition, the artemisinins may reduce gametocyte carriage and the transmissibility of malaria, which could contribute to malaria control in areas of low endemicity.

Piperaquine acts through the chemical inhibition of parasite haem detoxification and has a prolonged duration of action because of its very long half life.

In a three-day ACT regimen, the artemisinin component is present in the body during only two asexual parasite life-cycles for *P. falciparum*. While three days of artemisinin treatment greatly reduces the number of parasites in the body complete clearance is dependent on the partner medicine persisting at parasitocidal concentrations until all infecting parasites have been killed. Thus the partner compounds in ACT regimens need to be relatively slowly eliminated. In Eurartesim the applicant claims that DHA is

“protected” from resistance by PQP provided it is present at efficacious levels and that PQP is partly protected by DHA. Courses of one or two days of ACT are not recommended because they are less efficacious and provide less protection for the slowly eliminated partner drug (WHO 2006).

The relationship between plasma concentration and effect has not been assessed. Since the activity of the antimalarials is not exerted in plasma and since erythrocyte sequestration changes as the parasite load changes so investigations of effect related to plasma levels is not expected to be fruitful.

Secondary pharmacodynamic effects

The past experience and published data on the potential neurotoxic effects of DHA and the QT prolongation potential of DHA and PQP received particular attention during the clinical trial programme.

Neurotoxicity of artemisinins

In the Phase I/II studies no specific effects on neurological examinations were detected. There has been controversy regarding the neurotoxicity of artemisinin derivatives in man and animals. The potential for neurotoxicity in animals seems to be related to the dose, the route of administration and the PK properties of the different artemisinins (i.e. DHA and its pro-drugs). Sustained CNS exposure from slowly absorbed or eliminated artemisinins was shown to be more neurotoxic than intermittent brief exposure.

Thus, the oil-based derivatives that are given IM, such as artemether and arteether, appear to be more neurotoxic than the derivatives that are given orally or intravenously. The potential for neurotoxicity to occur in man with orally administered DHA (the active metabolite of all derivatives of the artemisinin class) was concluded to be low given its rapid clearance and use in a 3-day regimen.

QT prolongation by artemisinins

Various studies in animals with different artemisinins have shown a potential to cause prolongation of QTc intervals. Other changes in ECGs have been noted under some experimental conditions. PQ-associated AV block and prolongation of the PR and QRS durations have all been observed. The applicant conducted a study to compare the effects of PQ, chloroquine (CQ) and mefloquine on hERG tail current. Exposure to these agents reduced hERG residual tail current in a dose related manner and the dose response curves gave IC50 values of 5.28, 4.03 and 19.88 µM, respectively. Hence CQ and PQ have nearly identical hERG IC50 values.

During the procedure the applicant performed **study DM09-006 on QTc prolongation**. ECG manual readings performed by CardiaBase (Nancy, France) were to be made under blind conditions. The study initially planned to include 208 healthy subjects as follows:

Group 1 (64 subjects): Eurartesim at the standard dose after a high-fat/low-kcal (400 kcal) meal

3 doses over three days, each of 3 or 4 tablets by body weight

Eurartesim placebo on D-1

Group 2 (64 subjects): Riamet (artemether/ lumefantrine) at the standard dose, each dose after high fat/low kcal (400 kcal) meal

6 doses over three days, each of 4 tablets in the morning and evening;

Eurartesim placebo on D-2

Group 3 (40 subjects): Placebo (matching Eurartesim) after a high-fat/low-kcal (400 kcal) meal

Doses as in Group 1 followed by one dose of moxifloxacin (Izilox) 400 mg on D4 after a high-fat/low-kcal meal

Group 4 (40 subjects): Eurartesim at the standard dose after high-fat/high-kcal (1000 kcal) meal

Doses as in Group 1 but after a high-fat/high-kcal meal;

Eurartesim placebo on D-1

After conducting an interim analysis on the first four groups it was planned to enrol two additional groups (5 and 6) as follows:

Group 5 (40 subjects)

Subjects took 3 or 4 tablets (according to weight \leq 75 kg) of placebo on Day -1 and 3 or 4 tablets of Eurartesim once daily from Day 1 to Day 3 with intervals of 24 ± 0.5 h. Dosing was each morning at around 08:00 a.m. with water and without any food intake. Dosing was followed at 3 h by breakfast and at 6 h by lunch with a standard dinner around 08:30 p.m.

Group 6 (20 subjects)

Subjects took 3 or 4 tablets of placebo once daily from Day -1 to Day 3 and then 400 mg moxifloxacin on Day 4. Other dosing features were as for Group 5 except that moxifloxacin was given after a high-fat/low-Kcal meal.

For Groups 3 and 6 the largest mean effects of moxifloxacin on QTcF (Fridericia calculation method) were reported at 4 and 6 h post-dose. The lower 90% CI were 12.5 and 13.3 ms and so assay sensitivity was demonstrated.

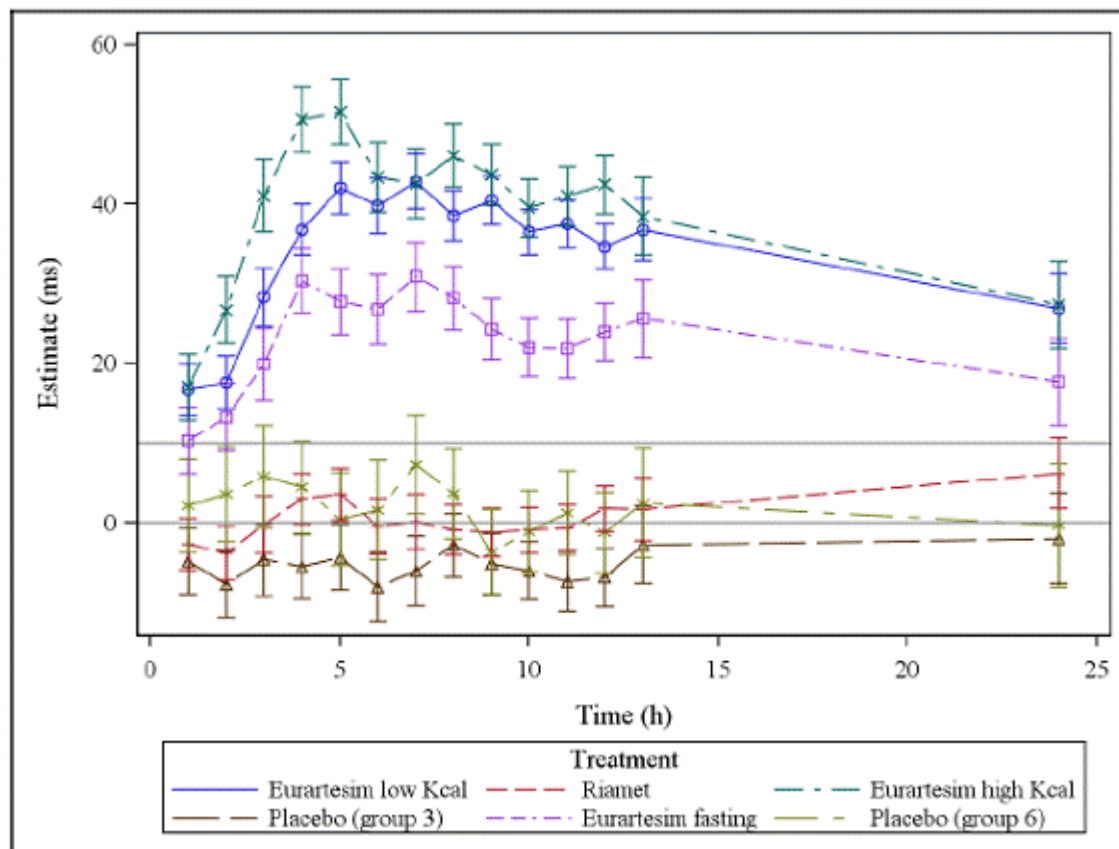
Table 21: Assay sensitivity (QTcF) – Maximum effect

| | | Izilox | | Placebo | | Estimates of $\Delta\Delta$ QTcF (Izilox-Placebo) | | |
|-------|------|---------------|------------|---------------|------------|---|------------|---------|
| Group | Time | Estimate (SE) | 90% CI | Estimate (SE) | 90% CI | Estimate (SE) | 90% CI | p-value |
| 3 | H4 | 12.0 (1.3) | 9.8; 14.2 | -3.5 (1.3) | -5.7; -1.3 | 15.5 (1.8) | 12.5; 18.4 | <.0001 |
| 6 | H6 | 19.5 (2.0) | 16.2; 22.9 | 2.1 (2.0) | -1.2; 5.5 | 17.4 (2.5) | 13.3; 21.5 | <.0001 |

Based on uncorrected QT data the comparisons with respective placebo groups were as shown in the figure and as follows:

- Group 1 (Eurartesim high-fat/low-Kcal) vs. placebo (group 3) 39.3 ms ($p < 0.0001$)
- Group 2 (Riamet) vs. placebo (group 3) 5.8 ms ($p = 0.0065$)
- Group 4 (Eurartesim high-fat/high-Kcal) vs. placebo (group 3) 38.9 ms ($p < 0.0001$)
- Group 5 (Eurartesim fasting) vs. placebo (group 3) 21.2 ms ($p < 0.0001$)

Figure 9: Estimate of treatments effect over time on time-matched changes in QT (ms)
– Triplicate ECG analysis set



In the placebo groups the mean maximum time-matched changes in QTcF were 10.6 ms for Group 3 and 12.8 ms for Group 6 while CV% appeared to be slightly lower for Group 6 (53% vs. 63%).

The contrast between estimated means of the maximum time-matched changes from baseline in QTcF between Group 1 (Eurartesim high-fat/low-Kcal) and Group 5 (Eurartesim fasting) was 12.6 ms with lower 95% CI 7.4 ms. Thus dosing in the fasting state had a lesser effect on QTcF.

Consequently while the comparison between Group 4 (Eurartesim high-fat/high-Kcal) and Group 2 (Riamet) was 36.1 ms, the difference was reduced to 13.4 ms (95% CI [-17.1; -9.7]) between Group 5 (Eurartesim fasting) and Group 2 (Riamet). Also, the contrast of the estimated means of the maximum time-matched changes from baseline in QTcF between Group 5 (Eurartesim fasting) and Group 6 (placebo) was 21.0 ms (95% CI [15.7; 26.4]). However, this still exceeded the difference observed on comparing Group 2 (Riamet) and Group 3 (placebo), which was 9.9 ms (95% CI [6.8; 12.9]).

As shown in the table below all the comparisons between treatments were statistically significant. The p-values were always < 0.0001 except for the comparison between Group 1 (Eurartesim high-fat/low-Kcal) and Group 4 (Eurartesim high-fat/high-Kcal) for which the p-value was 0.0025.

Stratification by body weight (*i.e.* comparing the subjects below or above 75 kg) did not change significantly the results. No significant interaction between body weight and treatment was detected and the estimates of treatment effects adjusted for body weight were consistent with those previously obtained.

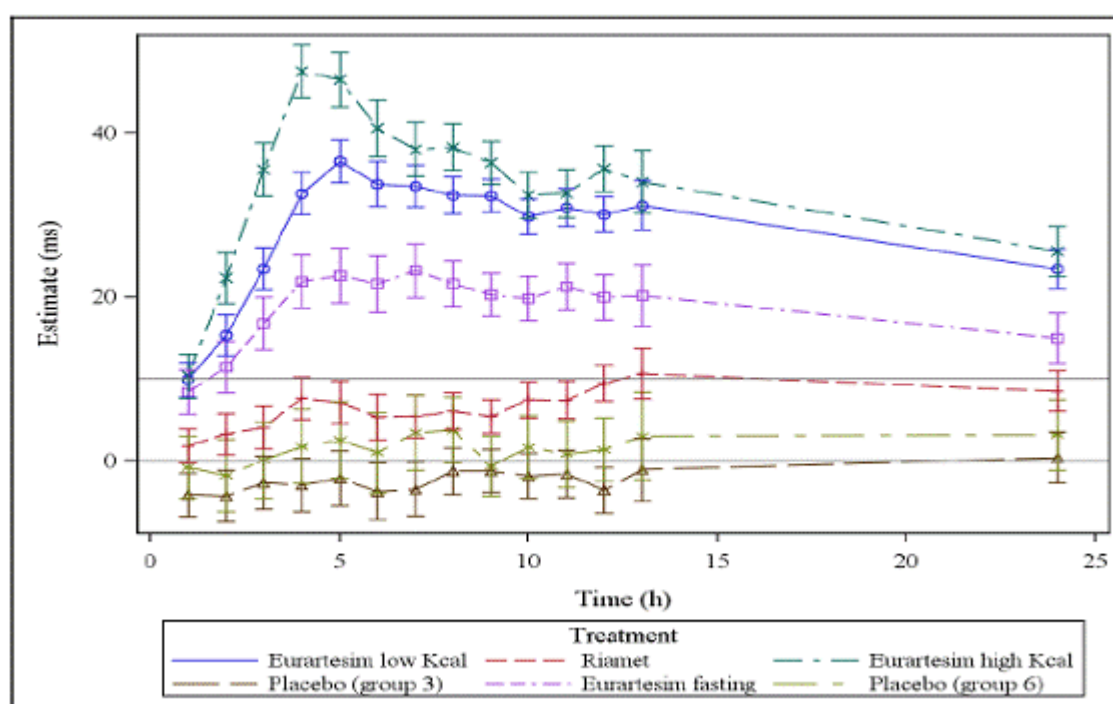
A statistical difference between genders across treatments was detected. Also, the effect of Riamet on QTc prolongation was nearly doubled in female vs. male subjects (maximum time-matched changes in QTcF of 7.9 ms in male and 13.1 ms in female subjects).

Table 22: All treatments comparisons for maximum time-matched changes in QTcF (ms) – Triplicate ECG analysis set

| Treatment 1 | | | Treatment 2 | | | Contrast (Treatment 1-Treatment 2) | | |
|----------------------|---------------|------------|----------------------|---------------|------------|------------------------------------|--------------|---------|
| Treatment | Estimate (SE) | 95% CI | Treatment | Estimate (SE) | 95% CI | Estimate (SE) | 95% CI | p-value |
| Eurartesim low-Kcal | 46.4 (1.4) | 43.6; 49.3 | Riamet | 20.4 (1.4) | 17.6; 23.3 | 26.0 (2.0) | 22.0; 30.0 | <.0001 |
| | 46.4 (1.5) | 43.5; 49.4 | Placebo (group 3) | 10.6 (1.9) | 6.9; 14.3 | 35.9 (2.4) | 31.1; 40.6 | <.0001 |
| | 46.4 (2.0) | 42.4; 50.4 | Eurartesim high-Kcal | 56.5 (2.5) | 51.5; 61.6 | -10.1 (3.2) | -16.5; -3.6 | 0.0025 |
| | 46.4 (1.6) | 43.2; 49.7 | Eurartesim fasting | 33.8 (2.1) | 29.8; 37.9 | 12.6 (2.6) | 7.4; 17.8 | <.0001 |
| Riamet | 20.4 (1.0) | 18.5; 22.3 | Placebo (group 3) | 10.6 (1.2) | 8.2; 13.0 | 9.9 (1.5) | 6.8; 12.9 | <.0001 |
| | 20.4 (1.7) | 17.1; 23.7 | Eurartesim high-Kcal | 56.5 (2.1) | 52.3; 60.7 | -36.1 (2.7) | -41.4; -30.8 | <.0001 |
| | 20.4 (1.2) | 18.1; 22.7 | Eurartesim fasting | 33.8 (1.5) | 30.9; 36.7 | -13.4 (1.9) | -17.1; -9.7 | <.0001 |
| Placebo (group 3) | 10.6 (2.2) | 6.1; 15.0 | Eurartesim high-Kcal | 56.5 (2.2) | 52.1; 61.0 | -46.0 (3.2) | -52.3; -39.6 | <.0001 |
| Eurartesim high-Kcal | 56.5 (2.4) | 51.7; 61.4 | Eurartesim fasting | 33.8 (2.4) | 29.0; 38.7 | 22.7 (3.5) | 15.8; 29.6 | <.0001 |
| Eurartesim fasting | 33.8 (1.5) | 30.7; 36.9 | Placebo (group 6) | 12.8 (2.2) | 8.4; 17.2 | 21.0 (2.7) | 15.7; 26.4 | <.0001 |

Comparison between Eurartesim low Kcal and Riamet is study's primary endpoint. Comparison between Eurartesim low Kcal and Eurartesim fasting is primary endpoint for the second study part. Other comparisons are secondary endpoints. All treatment comparisons were performed in separate models.

Figure 10: Estimate of treatments effect over time on time-matched changes in QTcF (ms) – Triplicate ECG analysis set



For the comparisons of the *time-averaged* time-matched changes in QTcF, these were:

- Group 1 (Eurartesim high-fat/low-Kcal) vs. Group 2 (Riamet) = 21.8 ms (LL 95% CI 19.1 ms)
- Group 4 (Eurartesim high-fat/high-Kcal) vs. Group 2 (Riamet) = 27.5 ms
- Group 5 (Eurartesim fasting) vs. Group 2 (Riamet) = 12.5 ms

The duration of a contrast > 20 ms was shorter for Group 5 compared to Groups 1 and 4 but the median times of occurrence of the maximum time-matched changes were roughly comparable for the three Eurartesim Groups (5 to 7.5 h post-dose) but 7-8 h post-dose for placebo and 11.5 h for Riamet.

With regard to the analysis of late ECGs at Day 4 (corresponding to 36 h post-dose) QTcF mean changes from baseline were all < 20 ms and varied from 15.9 ms (Group 1) to 12.2 ms (Riamet). At 120 h post dose all changes were between 3.4 and 5.5 milliseconds. Similar observations applied to the QTcB and QTcP datasets.

Corresponding analyses were performed for the QTcB (Bazett calculation method) and QTcP datasets. The categorical analysis of QTcF, QTcB and QTcP demonstrated that no subjects had QTc values above 450 ms in the two placebo groups. In the Riamet group one subject had a QTc value between 450 and 480 ms, regardless of the corrective method, and another subject had only a QTcB value between 480 and 500 ms. In the Eurartesim groups 23.4% (15/64) in Group 1 had maximum QTcF values above 450 ms and 10.0% (4/40) in Group 5. No values above 500 ms were recorded throughout the study.

There were no changes from baseline in QTcF values that exceeded 30 ms in the two placebo groups and 7.8% (5/64) in the Riamet group had such a change. In contrast the Eurartesim groups included 89% (57/64) in Group 1 and 95% (38/64) in Group 4 with changes > 30 ms compared to 65% (26/40) of subjects who were dosed in the fasting state.

The contrast of the estimated means of the maximum time-matched changes in **RR** between Groups 1 and 4 vs. Group 3 (placebo) were 61.8 ms and 48.1 ms, respectively, while the contrast between Group 5 (Eurartesim fasting) and Group 6 (placebo) was 24.3 ms. However, the differences between the three Eurartesim groups and the Riamet group were 76.3 ms, 62.6 ms and 70.6 ms, respectively. A similar pattern of observations applied to the estimated time-averaged time-matched changes in RR.

The estimated means of the maximum time-matched changes from baseline in **HR** showed only small actual differences between groups. Nevertheless several of the comparisons made reached significance as shown in the table below and the figure suggests that in comparison to placebo HR tended to be higher with Riamet and lower with Eurartesim regardless of the dosing conditions.

The comparisons in maximum time-matched changes in **PR** revealed no statistically significant differences between the treatments. Similarly, the analysis of the maximum time-matched changes in **QRS** showed no statistically significant differences were observed between the treatments.

A correlation analysis for QTcF values and PQ PK parameters considered the following variables:

- QTcF maximum time-matched changes from baseline to Day 3 and the values of Cmax and AUC0-24 at Day 3 within study DM09-006 (low and high/kcal meal)
- QTcF changes from Day 0 (h 0) to Day 2 (h 0) and the values of Cmax and AUC0-24 at Day 1, combining the data of study DM09-006 (low and high/kcal meal) and study DM04-009 (fasting conditions)

The results obtained for Cmax and AUC0-24 were closely comparable with a slightly stronger correlation for the latter. In the figure below the AUC0-24 values for subjects with malaria in study DM04-009 (Part a of the figure; Eurartesim without concomitant food) and subjects enrolled in study

DM09-008 (Part b of the figure; Eurartesim under fasting conditions) have been projected along the QTcF/PK regression line estimated within study DM09-006.

The AUC₀₋₂₄ values for studies DM04-009 and DM09-008 were available only for Day 1. Therefore, these values were multiplied by a conversion factor of three to obtain exposure parameters for Day 3. The conversion factor was estimated after pooling data from all available PK studies and was deemed to be conservative because it tended to overestimate Day 3 plasma exposure.

Correlation analysis (95% individual prediction boundaries) between QTcF maximum time-matched changes from baseline to D3 and PQ AUC₀₋₂₄ at D3 within study DM-09-006 (Low & High/kcal)

Figure 11

Part a) DM04-009 (Eurartesim taken without concomitant food)

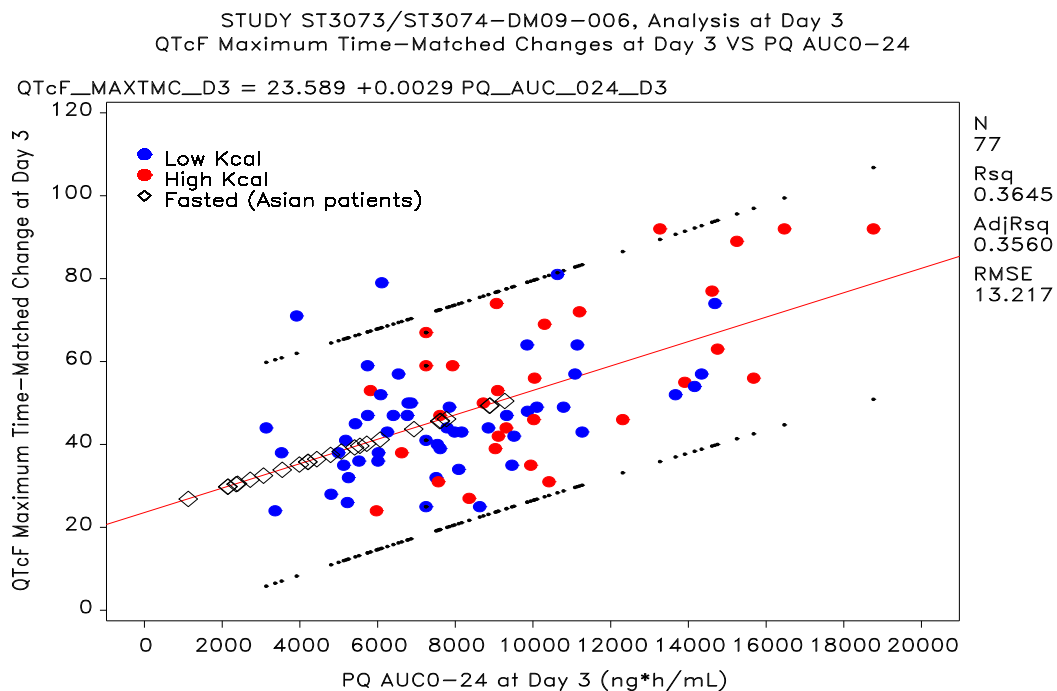
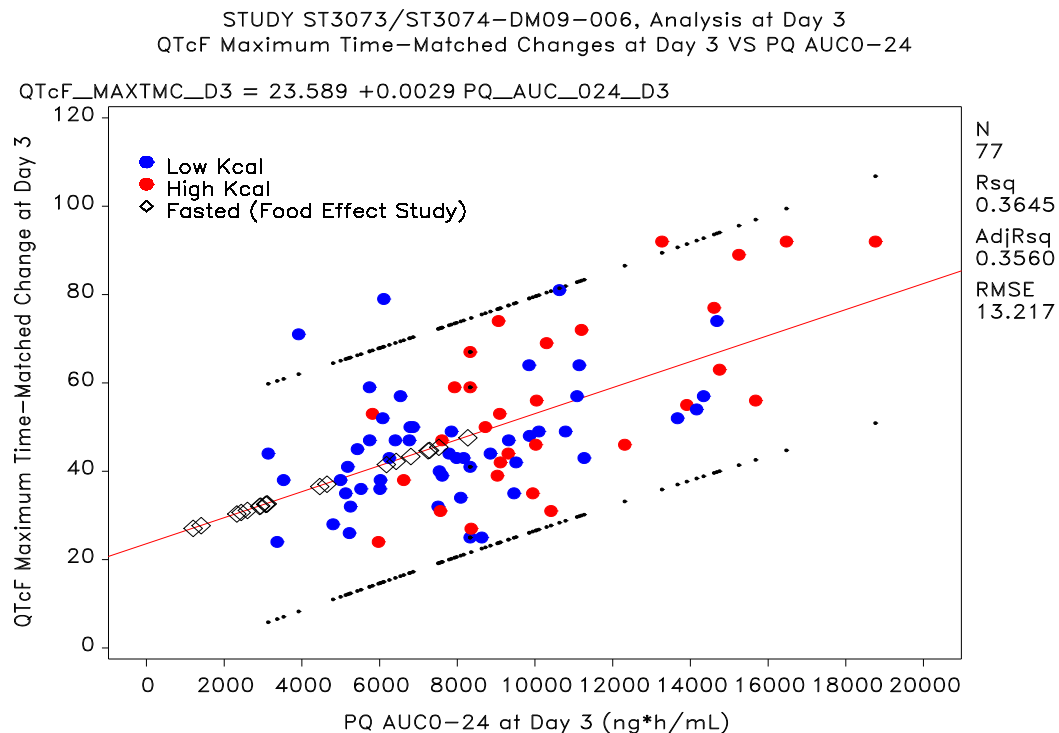


Figure 12

Part b)

DM09-008 (Fasting conditions)



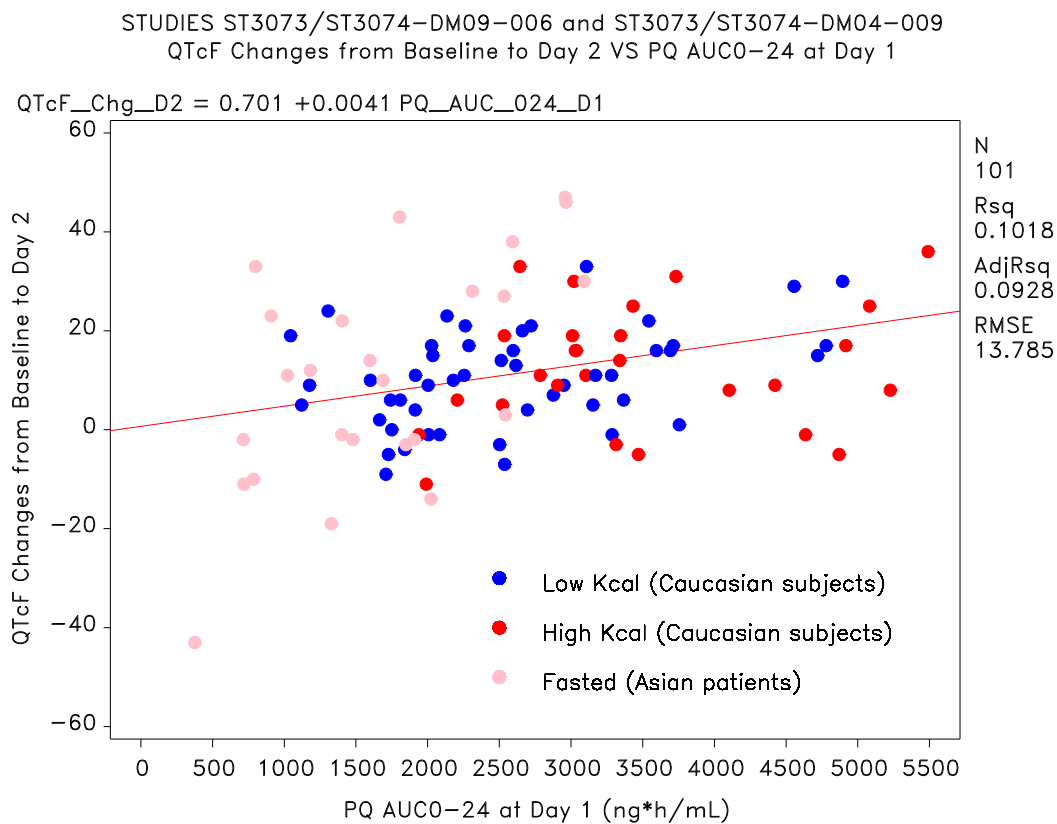
From these figures the applicant concluded that:

- There is a statistically significant correlation between the peak values of QTcF changes from baseline and PQ AUC0-24 within DM09-006 (correlation coefficient equal to 0.60; $p < 0.0001$).
- On average, the predicted maximum QTcF time-matched changes for subjects taking Eurartesim under fasting conditions or without concomitant food are lower than the observed QTcF changes for subjects taking Eurartesim in fed conditions.
- Approximately 75% of the predicted maximum QTcF time-matched changes from baseline for the subjects taking Eurartesim under fasting conditions or without concomitant food are located in an area of the regression line where the upper prediction boundary is below 60 ms. The remaining patients/subjects (approximately 25%) have AUC0-24 values compatible with a predicted maximum QTcF time-matched change from baseline potentially higher than 60 ms.
- The plots for healthy subjects and those with malaria appear to be super-imposable.

The results shown in the next figure show a trend that is comparable to that in the previous analyses although to a lesser degree. The applicant points out that the limitation of this analysis is the QTcF change from D0 to D2, which measures the effect of Eurartesim after 12 h from the last treatment intake.

Correlation analysis between the QTcF changes from baseline to D2 and PQ AUC0-24 at D1 combining DM09-006 (low and high/kcal meal) and DM04-009 (Without concomitant food)

Figure 13



2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of PQP were characterised by a slow absorption process (its absorption being influenced by food) and a very long half life of about 22 days. The long half-life is mainly due to the very large volume of distribution observed in patients. PQP is poorly and very slowly metabolised in humans.

The pharmacokinetics of DHA were characterised by rapid absorption and elimination. DHA volume of distribution was quite low; it is known that DHA accumulates in erythrocytes. DHA was cleared mainly by phase II metabolism to the glucuronide which was the main metabolite observed *in vitro* and *in vivo*.

PQP undergoes enterohepatic recirculation and its absorption was influenced by food intake.

The effect of food on DHA absorption was investigated in a food interaction study to evaluate the effect of food on both DHA and PQ after a single oral dose of Eurartesim in healthy male volunteers having a body weight ≥ 75 kg (ST3073 ST3074-DM09-008). A food effect for Eurartesim was found for both DHA and PQP, on comparing the pharmacokinetic parameters administration following a high fat meal compared with administration in the fasted state. This was clinically significant for PQP only.

Comparing the PQP pharmacokinetic parameters observed in this study and in adult patients, the administration of Eurartesim without food is suggested, avoiding the overexposure caused by concomitant food effect. The safety implications of different dosing conditions became apparent following results obtained in newly conducted trial DM09-006, which showed a significant QTcF interval prolongation effect compared to comparator (Riamet). This effect appeared to be emphasised by the concomitant intake of Eurartesim with food which in turn increases the plasma concentration of PQP

The effect of concomitant administration of Eurartesim and known CYP3A4 inhibitors has not yet been studied. In clinical trials conducted by the applicant, no difference in the safety profile of Eurartesim became apparent in patients taking antibacterials, antimycotics and antivirals, when compared to patients not exposed to these drugs. Nevertheless, the applicant has committed to perform three drug-drug interaction studies with Eurartesim and other drugs that are metabolized via CYP 3A4 (clarithromycin, midazolam) and an oral contraceptive (ethinyl estradiol and levonorgestrel). These studies are listed in the pharmacovigilance plan.

Data is currently missing from certain populations, including the European malaria patient population and in particular Caucasian malaria patients. In healthy volunteer studies, 258 Caucasian subjects were exposed to Eurartesim to date. Results from study ST3073/ST3074- DM09-007 revealed there were no differences in PK between healthy Caucasian and healthy Asian volunteers.

2.4.5. Conclusions on clinical pharmacology

Data have shown that Eurartesim has a QT prolongation effect, especially if taken with food. Hence, QTc prolongation is an identified important safety risk stated in the RMP. To minimise the potential risk of cardiac arrhythmias, Eurartesim is contraindicated in patients who might be at particular risk of developing cardiac arrhythmias. Additional risk minimisation measures are planned in this regard (educational outreach programme to health care workers).

Neurotoxicity, albeit unlikely with orally administered DHA, is a potential concern flagged in the Risk Management Plan (RMP).

Missing data relate to some special populations and to drug interaction with CYP 3A4 metabolised drugs / other antimalarial medicines. These concerns are noted in the RMP.

2.5. Clinical efficacy

2.5.1. Dose response studies

There were no dose-finding studies. The dose ratio of DHA and PQP and the dose regimen used for adults and children in the two pivotal Phase III studies were selected based on previous published studies.

2.5.2. Main studies

- Data on the efficacy of Eurartesim in patients with uncomplicated *P. falciparum* malaria were collected in four studies as shown in the table below.
- The efficacy data available from the two Phase I/II studies were very limited.

Table 24: Tabular Listing of the Sigma-Tau Clinical Studies to Support the Registration of Eurartesim for Treatment of Uncomplicated *P. falciparum* Malaria.

| Study | Dose* | Test Regimen | Comparator | Total No. of Subjects | Subject Type | Main Efficacy Endpoint | Status |
|---|---|--|---|-----------------------|---|---|-----------|
| ST3073+ST3074 DM 04008 (Africa) Phase I/II | Dose range: 1.67-3.08 mg/kg/day DHA and 13.3-24.64 mg/kg /day PQP | 20 mg DHA/160 mg PQP or 40 mg DHA/ 320 mg PQP tablet. 3 oral doses in 48 hrs. | Not Applicable | 32 | Paediatric <i>P. falciparum</i> malaria patients | To assess the PK of DHA and PQP by analysing serial blood samples during and after a therapeutic course in children with malaria | Completed |
| ST3073+ST3074 DM04009 (Asia) Phase I/II | Dose range: 1.6-3.64 mg/kg/day DHA and 12.8-29.12 mg/kg/day PQP | 40 mg DHA/320 mg PQP tablet. 3 oral doses in 48 hrs. | Not Applicable | 25 | Adult <i>P. falciparum</i> malaria patients | To assess the pharmacokinetics of DHA and PQP by analysing serial blood samples during and after a therapeutic course in adults with malaria. | Completed |
| ST3073+ST3074 DM040010 (Asia) Phase III | Dose range:1.67-3.33 mg/kg/day DHA and 13.3-26.7 mg/kg /day PQP | 20 mg DHA/160 mg PQP or 40 mg DHA/320 mg PQP tablet. 3oral doses in 48hrs. | 50 mg AS +250 mg MQ AS 4 mg/kg/day for 3 days + MQ 25 mg/kg divided into two doses | 1150 | Adult and paediatric <i>P. falciparum</i> malaria patients (even in combination with other Plasmodia) | To demonstrate that the PCR-corrected cure rate of DHA/PQP at Day 63 is non-inferior to that of AS+MQ (non-inferiority margin=5%) | Completed |
| ST3073+ST3074 DM040011 (Africa) Phase III | Dose range: 1.6-3.64 mg/kg/day DHA and 12.8-29.12 mg/kg/day PQP | 20mg DHA/160mg PQP or 40mg DHA/320 mg PQP tablet 3 doses in 48 hrs | 20 mg A/120 mg L 2-6 tablets per day over 3 days dependant on body weight | 1553 | Paediatric <i>P. falciparum</i> malaria patients | To demonstrate that the PCR-corrected cure rate of DHA/PQP at Day 28 is non-inferior to that of A/L (non-inferiority margin=5%) | Completed |

Each main phase III study included the following:

Clinical Development Committee (CDC): The CDC primarily addressed the scientific conduct, ethical integrity and regulatory acceptability of the programme and comprised one representative from Medicines for Malaria Venture (MMV), two from Sigma-Tau and the Co-ordinating Investigators of each of the two Phase III studies.

Study Steering Committee (SSC): The SSC reported to the CDC and was responsible for protecting the scientific conduct and integrity of the study. The SSC included at least one investigator from each participating region in addition to the Co-ordinating Investigator.

Data Monitoring Committee (DMC): The DMC was responsible for performing an interim analysis for sample size reassessment, monitoring all safety data during the course of the study and revising the

primary efficacy data. The DMC included one statistician and four clinicians with malaria expertise who were independent of Sigma-Tau and MMV.

Study DM040010 (Asia study)

A Phase III, Randomised, Non-Inferiority Trial, to Assess the Efficacy and Safety of Dihydroartemisinin/Piperaquine (DHA/PQP, ArtekinaTM) in Comparison with Artesunate + Mefloquine (AS+MQ) in Patients Affected by Acute, Uncomplicated *P. falciparum* Malaria

Methods

This was a multi-centre, randomised, open label, two-arm parallel group study to determine whether DHA/PQP was non-inferior to AS+MQ and to assess its safety and tolerability in Asian patients (adults and children) with acute uncomplicated *P. falciparum* malaria. DM 040010 was conducted between June 24 2005 and 7 April 2007 at 10 study sites spread across India (3), Laos (2) and Thailand (5).

Study Participants

DM 040010 was to enrol subjects aged between 3 months and 65 years (excluding pregnant or lactating women) of body weight ≥ 5 kg who had microscopically confirmed mono-infection with *P. falciparum* (parasitaemia 80 - 200,000/ μ L) or mixed infection in which the *P. falciparum* component was to be 80-200,000/ μ L. They were also to have a history of fever or presence of fever (temperature $\geq 37.5^{\circ}\text{C}$).

Depending upon local practice, patients were admitted to hospital for either three or seven days and then followed up as out-patients or all study visits were conducted as out-patients. The study report states that the design of the study followed the 2003 WHO guidance regarding the minimum durations of follow up according to local transmission. The study used the WHO-recommended follow-up periods for regimens involving MQ (63 days) to accommodate the half-life. In addition, molecular genotyping using PCR technology was used to distinguish between recrudescence and new infections and parasite clearance was assessed from thick and thin blood smears.

Treatments

Subjects were randomised to DHA/PQP or comparator AS/MQ (Artequin).

Artequin was manufactured by Mepha, Switzerland.

- **DHA/PQP and AS** were each given orally once daily for three days. The daily dose of AS was 4 mg/kg/day which equated to four 50 mg tablets/day for a 50 kg person or 4 ml/day of a 10 mg/mL suspension (actually given as crushed or dissolved tablets in water) for a 10 kg child.
- **MQ** was given once daily with AS on the second and third day of AS dosing. The dose of MQ was 25 mg/kg divided into two doses, which equated to a total of five 250 mg tablets for a 50 kg person or 5 mL of a 50 mg/mL suspension (dissolved tablets in water) for a 10 kg child.

Doses were calculated by body weight as shown in the table below.

Table 24: DHA/PQP Dosing Regimen

| Body weight (kg) | DHA Dose/Tablet (mg) | PQP Dose/Tablet (mg) | No. Tablets/Dose or/Day |
|------------------|----------------------|----------------------|-------------------------|
| 4* - 6 | 10 | 80 | ½ ** |
| 7 - 12 | 20 | 160 | 1** |
| 13 - 23 | 40 | 320 | 1 |
| 24 - 35 | 80 | 640 | 2 |
| 36 - 75 | 120 | 960 | 3 |

*5 kg was the minimum weight required for study entry. **Paediatric tablet

Dosing was with water and without regard to last food intake. Patients were observed for one hour after dosing to ensure that the medication was not vomited or spat out. If the dose was vomited within 30 minutes of dosing, a further full dose was given. If the dose was vomited between 31 and 60 minutes after dosing, a further half dose was given. Patients who vomited twice were withdrawn.

During the study the following treatments were forbidden:

- Any other anti-malarial treatment.
- Antibacterial agents with antimalarial activity (e.g. erythromycin or other macrolides, co-trimoxazole or other sulfonamides, any tetracycline, quinolones, clindamycin).

Patients were withdrawn from the study if any of the above drugs were taken.

Chloroquine was allowed for the treatment of non-*falciparum* infections occurring during follow up.

Parents and parents/guardians were discouraged from obtaining drugs from private pharmacies or physicians.

Rescue Treatments

Patients with treatment failure were withdrawn from the study, treated and followed up as per local practice. They did not have to undergo efficacy evaluation thereafter. Patients requiring rescue therapy were treated with AS 2 mg/kg/day orally for seven days plus doxycycline (if there was no contraindication) in accordance with the recommended second-line antimalarial treatment in the WHO 2006 treatment guideline. Any patient diagnosed with severe malaria or danger signs during follow-up was referred for treatment with parenteral artesunate and supportive measures at the local facility or hospital.

Objectives

The study aimed to demonstrate that the PCR-corrected cure rate of DHA/PQP was non-inferior to that of the comparator. This cure rate was defined as the proportion of patients with adequate clinical and parasitological response (ACPR) at Day 63 plus those treatment failures (TFs) identified as new P. falciparum (by PCR) and non-falciparum infections.

In order to compare the study results with the historical ones, the criteria described by WHO (2003) were used. These failure rates computed in each treatment group were judged against the efficacy threshold of 90% (WHO 2006). An efficacy threshold of <90%, obtained in an analysis carried out in accordance with the WHO requirements, indicates that a treatment should not be considered for first-line treatment policy.

Outcomes/endpoints

Thick and thin Giemsa stained blood smears were obtained to verify the presence of *P. falciparum* and to calculate asexual and sexual parasite density. Films were examined at the study site with a binocular light microscope under oil immersion at 1000x magnification. At least 100 thick film fields were examined. Counting was based on at least 200 leucocytes on the thick blood film according to WHO standards. The parasite density was calculated according to standard formulae.

Blood smears were collected using kits provided by MDS and a proportion was randomly chosen for QC testing. However, errors at MDS resulted in its replacement by Muhimbili University of Health and Allied Sciences, Department of Parasitology & Medical Entomology, Dar Es Salaam, Tanzania. The Data Monitoring Committee (DMC) was responsible for evaluating the findings.

PCR was used to genotype *P. falciparum* at the Prince Leopold Institute of Tropical Medicine (ITM) in Antwerp, Belgium. The QC plan was for 20% to be re-analysed at the MDS Central Laboratory in Beijing but this laboratory did not use the same procedures and therefore the SMRU in Thailand was appointed instead. All PCR gels were also read by an independent expert (Paris). The DMC was responsible for providing a critical evaluation of the findings.

The study aimed to demonstrate that the **PCR-corrected cure rate** of DHA/PQP was non-inferior to that of the comparator. This cure rate was defined as the proportion of patients with adequate clinical and parasitological response (ACPR) at **Day 63** plus those treatment failures (TFs) identified as new *P. falciparum* (by PCR) and non-*falciparum* infections.

ACPR was defined as absence of parasitaemia through to Day 63 irrespective of temperature and not meeting any of the criteria for early treatment failure (ETF) or late clinical (LCF) or parasitological failure (LPF). TF was defined as the sum of early and late TFs (ETF+LTF).

ETF was defined as:

1. Development of danger signs or severe malaria on Days 0, 1, 2 or 3, in the presence of parasitaemia.
2. Parasite density on Day 2 > Day 0 count, irrespective of temperature.
3. Presence of parasitaemia on Day 3 with fever (temperature $\geq 37.5^{\circ}\text{C}$).
4. Parasitaemia on Day 3 $\geq 25\%$ of count on Day 0.

LTF could be due to Late Clinical Failure (LCF) or Late Parasitological Failure (LPF):

LCF was defined as:

1. Development of danger signs or severe malaria after Day 3 in the presence of parasitaemia.
2. Presence of parasitaemia and fever on any day from Day 4 to Day 63, without previously meeting the criteria of ETF or LCF.

LPF was defined as reappearance of parasitaemia after initial clearance between Day 7 and Day 63 (identified as recrudescence by PCR analysis) in the absence of fever (temperature $< 37.5^{\circ}\text{C}$) without previously meeting the criteria of ETF or LCF.

According to the protocol, efficacy analyses were to be performed on the pure Intention-To-Treat (pure-ITT; all treated), modified ITT (m-ITT; pure-ITT population with the exclusion of those patients lost-to-follow up for unknown reasons before Day 63) and the Per Protocol (PP; pure-ITT with no major protocol violations) populations. The m-ITT and the PP populations were the co-primary populations

Sample size

The sample size was initially computed using the original formulation of the primary objective (with two co-primary objectives) which required a simulation. From this simulation it was concluded that if the PCR-corrected cure rate at Day 63 in the ITT population was in the range of 92-95% for AS+MQ, a sample size of 350 patients in the AS+MQ arm and 700 patients in the DHA/PQP arm (1050 patients in total) was needed. With the third protocol amendment a new formulation of the sample size requirement was written.

Randomisation

A randomisation list was generated before the study started. Treatment allocation was concealed until the subject had completed the screening procedures and was deemed eligible for the study. The treatment allocation was contained in a sealed envelope. A procedure was established for opening a sealed envelope.

Subjects were randomised to either DHA/PQP or AS+MQ in a 2:1 ratio

Blinding (masking)

This was a randomised open label study. The study used an open label design because of the complexity of establishing a double-blind dosing schedule involving placebo tablets of DHA/PQP and placebo tablets of AS+MQ. Procedures to minimise bias in the treatment comparison, especially to reduce the investigator's bias and the bias in the assessment of the primary endpoint are described.

All decisions pertaining to the allocation of patients to various analysis populations and the assessment of the primary endpoint were conducted in blinded conditions and without knowledge of the PCR results.

Statistical methods

The lower limit of the one-sided 97.5% confidence interval (CI; = lower limit of the two-sided 95% CI) for the treatment difference in the percentage of PCR-corrected cure rates (ACPR) at Day 63 was computed. In order to confirm non-inferiority of DHA/PQP versus the comparator the CI lower limit was to be >-0.05 (i.e. within -5%) in both the m-ITT and the PP populations.

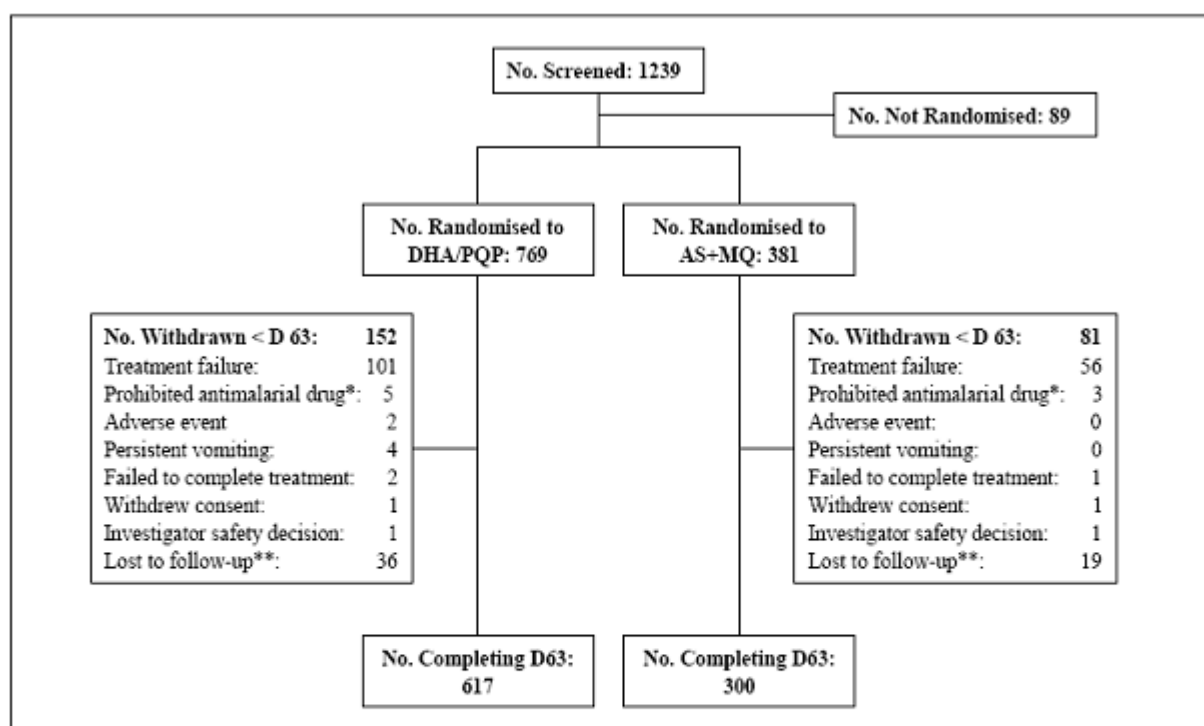
The PCR-corrected cure rates at Day 63 were to be described by country. The Breslow-Day test (if each country has at least two failures for each treatment) or logistic regression (otherwise) were to be used to evaluate homogeneity across countries. A similar approach was taken to analysis of outcomes by age groups.

A range of sensitivity analyses was pre-defined. These included analyses in which:

- All patients with missing parasitaemia were treated as failures
- All patients with new infections as detected by PCR were excluded from the analysis (this analysis was added *post hoc*) following the suggestion of the study investigators.

Results

Participant flow (Figure 14)



Source: Tables 10.1.1a, 10.1.2 and Listings 10.1.1 and 10.1.3.

* Five patients in the DHA/PQP group (12018, 12120, 12129, 12155 and 43024) and three patients in the AS+MQ group (12005, 12090 and 12119) were not analysed as informative withdrawals because they did not take prohibited drugs, even if they were reported as such in the EOS dataset.

** An additional five patients in the DHA/PQP group (19062, 19068, 19070, 19071 and 19075) and one patient in the AS+MQ group (19073) were analysed as lost to follow-up before or at Day 63 on the basis of their parasitaemia evaluations. So 41 patients in the DHA/PQP group and 20 patients in the AS+MQ group were analysed as lost to follow-up.

Recruitment

In the Asian study, patients were recruited from India, Laos and Thailand. The distribution by country is presented in table 21 below:

Table 25: Patient Accountability by Country - Study ST3073+ST3074 DM040010 (Safety/ITT Population)

| Country | DHA/PQP | | AS+MQ | |
|-------------------|---------|-------|-------|-------|
| | n | % | n | % |
| Safety/ITT | 767 | | 381 | |
| India | 101 | 13.17 | 49 | 12.86 |
| Laos | 200 | 26.08 | 98 | 25.72 |
| Thailand | 466 | 60.76 | 234 | 61.42 |

Conduct of the study

Overall there were four (stated in the study report but five actually listed) general protocol amendments, one country-specific protocol amendment for India and one site-specific amendment for SMRU in Thailand. Other changes in the study conduct versus the protocol were found *a posteriori*. These included lack of standardisation of randomisation procedure, missed visit assessments, slight changes in the definition of parasite clearance and in the lay-out of the mock tables/listings and the addition of some statistical analyses not planned in the SAP.

General Protocol Amendments

The final protocol (10 January 2005) was amended twice before and three times after enrolment had started. The three amendments after enrolment had started were as follows:

24 November 2005

The DMC advised harmonising the statistical approaches for the two Phase III studies. In addition, the DMC had concerns about the co-primary endpoint *the cure rate of DHA/PQP must be at least 90%* and considered that it was necessary to distinguish between the two objectives of proving non-inferiority and of comparing the results with historical ones. As a consequence power was recalculated for each objective separately.

For the Non-Inferiority Analyses

The clinical and statistical specifications for the sample size computations were as follows:

- Primary endpoint = PCR corrected cure rate at Day 63
- Primary analysis = based on 97.5% one-sided CIs for the difference in cure rates
- Alpha = 0.025 (one-sided)
- Power = 80% (for a null hypothesis of a treatment difference worse than -5% and an alternative hypothesis of 0 difference between treatments)
- PCR-corrected cure rate of DHA/PQP and AS+MQ in the pure-ITT population at Day 63 = at least 92%
- Non-inferiority margin for the difference (test-reference) = -0.05 (equivalent to -5%)
- Randomisation: based on a 2:1 allocation scheme (test vs. reference).
- Rate of patient attrition in the m-ITT population compared to pure-ITT (i.e. rate of non-informative withdrawals) = 5%. Expected 63 day PCR corrected cure rate in mITT = 93%.

- Rate of patient attrition in the PP population compared with the ITT population (i.e. rate of withdrawals for any reason and protocol violations) = 20%. Expected 63 day PCR corrected cure rate in this population = 95%
- Primary analysis populations = both the m-ITT and the PP populations.

With these assumptions the sample size of 1050 patients (700 DHA/PQP and 350 AS+MQ) provided a power of approximately 80% for the lower bound of a 97.5 one-sided CI for the treatment difference being above -0.05 in the m-ITT and 84% for the same analysis in the PP population (for the power calculation both continuity correction and the inequality of variances under the null hypothesis were considered).

For the Historical Comparisons

A secondary objective of the study was that of estimating the failure rates within each treatment group in accordance with WHO criteria. The clinical and statistical specifications for the sample size computations for this analysis were as follows:

- Anticipated population proportion of clinical failures = as high as 10%
- Confidence level = 95% (two-sided interval)
- Precision = 5 percentage points.
- Rate of patient attrition in the PP population as compared to the ITT population (i.e. rate of withdrawals for any reason and protocol violations) = 20%.

According to WHO (2003) a sample size of at least 175 patients would be required in each treatment group for estimating the proportion of clinical failures to within a 5 percentage point of the true value with 95% confidence.

This amendment also acknowledged that:

- China would not be participating.
- The number of sites in Laos would increase from one to two.
- There would be no stratification by age in the study.
- Persistent vomiting occurring on any day, not just Day 0, was a withdrawal criterion.

13 September 2006

This was required because delays in obtaining Thai regulatory approval for two of the five centres resulted in patients being recruited over two malaria seasons. Thus it was necessary to add testing for any cohort effect to the statistics section.

27 December 2006

This was required to increase the total number of patients to be recruited to from 1050 to 1150 (767 DHA/PQP, 383 AS+MQ) to fulfil an Indian regulatory requirement to ensure that at least 100 patients recruited from Indian sites were exposed to DHA/PQP.

Thailand SMRU

This protocol amendment (6 January 2006) was required because the Thai MoPH EC did not want children to be recruited to the study: only adults aged ≥ 18 years could be included.

India Country Specific

This protocol amendment (21 April 2006) was required in order to accommodate local practices as follows:

- Recruitment restricted to adults aged ≥ 18 years.
- Prohibition of chloroquine during the study because it was still effective against *P. falciparum* in some regions of India.

Baseline data

Approximately 75% of the study population was male, all were Asian, the mean age was approximately 25 years and the mean body weight was 44 kg. In Laos the means were lower because both adults and children were recruited to the study while only adults were enrolled in India and few children were recruited in Thailand before the implementation of a protocol amendment restricting the study to adults. In Laos approximately 60% were male compared with approximately 80% in India and Thailand.

Geometric mean baseline parasite density was slightly higher in the AS+MQ treatment group compared with the DHA/PQP group in all study populations. Baseline parasite density also varied between countries, with the highest densities occurring in Laos and the lowest densities occurring in India.

Numbers analysed

The datasets analysed were as follows:

Table 26:

| | ST3073+ST3074 DM040010 | | | |
|-----------------|-----------------------------------|----------|--------------|----------|
| Data Set | DHA/PQP | | AS+MQ | |
| | n | % | n | % |
| Randomized | 769 | | 381 | |
| Safety | 767 | 99.74 | 381 | 100 |
| ITT | 767 | 99.74 | 381 | 100 |
| m-ITT | 726 | 94.41 | 361 | 94.75 |
| PP | 668 | 86.87 | 336 | 88.19 |
| | | | | |

Outcomes and estimation

In the primary analysis the comparisons of PCR-corrected and uncorrected cure rates resulted in 97.5% CI within -3.1%, with and without continuity corrections. The differences between uncorrected cure rates were statistically significant in the m-ITT ($p = 0.006$) and PP populations ($p=0.002$) in favour of Eurartesim and the one-sided 97.5% CI exceeded zero for all comparisons of uncorrected cure rates.

Table 27: Summary of Cure Rates at Day 63 – (All Populations)

| Study Population | Cure Rate | DHA/PQP | | AS+MQ | | Treatment Difference (DHA/PQP - AS+MQ) | | | |
|-----------------------------------|---------------|---------|-------|-------|-------|--|-----------------------------------|----------------------------|--------------------|
| | | n | % | n | % | Δ | Lower Limit of one-sided 97.5% CI | | Chi-square test, p |
| | | | | | | | Without Continuity Correction | With Continuity Correction | |
| Pure-ITT (n = 767, 381) | PCR-corrected | 674 | 87.87 | 330 | 86.61 | 1.26% | -2.87 % | -3.06% | 0.544 |
| | Uncorrected | 516 | 67.28 | 227 | 59.58 | 7.70% | 1.75 % | 1.56 % | 0.010 |
| m-ITT (n = 726, 361) | PCR-corrected | 704 | 96.97 | 344 | 95.29 | 1.68% | -0.84% | -1.04% | 0.161 |
| | Uncorrected | 516 | 71.07 | 227 | 62.88 | 8.19% | 2.22% | 2.01% | 0.006 |
| PP (n = 668, 336) | PCR-corrected | 659 | 98.65 | 326 | 97.02 | 1.63% | -0.39% | -0.61% | 0.074 |
| | Uncorrected | 504 | 75.45 | 223 | 66.37 | 9.08% | 3.07% | 2.84% | 0.002 |

The effects of implementing the various pre-planned input strategies for patients who were lost-to-follow-up and patients without a valid PCR result (pure-ITT population) gave PCR-corrected cure rates that ranged from 90.55 - 97.25% for the DHA/PQP group and from 89.24 - 96.33% for the AS+MQ group. For all strategies, the 97.5% one-sided CI was within -5%.

The sensitivity analysis in which patients with missing parasitaemia results were classified as TFs resulted in a difference in PCR-corrected cure rate between treatments that was not statistically significant. The 97.5% one-sided CI was within -5% in the m-ITT and PP populations. The difference between the treatment uncorrected cure rates was statistically significant but the cure rates were lower.

Excluding patients with new infection detected by PCR reduced the PCR-corrected cure rates but the 97.5% one-sided CI was within -5% in all populations. There was a higher proportion of new infections in the AS+MQ group compared with the DHA/PQP group.

Rates of recrudescence infections were low. In the m-ITT, the proportion of patients classified as recrudescence because of withdrawal or TF before Day 4 was 1.1% in the DHA/PQP group and 0.8% in the AS+MQ group. In the PP population the proportions with new *P. falciparum* infections were comparable between treatments but the proportions with infections due to other plasmodia were 12.9% in the DHA/PQP group compared to 19.3% in the AS+MQ group.

Table 28: Details of the Classification of Patients by PCR-Corrected Cure Rates (ACPR) at Day 63 – DHA/PQP (All Populations)

| Patient Classification | Pure-ITT (n = 767) | | m-ITT (n = 726) | | PP (n = 668) | |
|---|-----------------------|-------|--------------------|-------|-----------------|-------|
| | n | % | n | % | n | % |
| Recrudescence by PCR | 9 | 1.17 | 9 | 1.24 | 9 | 1.35 |
| Recrudescence due to informative withdrawal or failure before Day 3 | 49 | 6.39 | 8 | 1.10 | 0 | - |
| Imputed as Recrudescence* | 35 | 4.56 | 5 | 0.69 | 0 | - |
| New <i>P. falciparum</i> Infection by PCR | 70 | 9.13 | 70 | 9.64 | 69 | 10.33 |
| Malaria Infection \neq falciparum** | 88 | 11.47 | 88 | 12.12 | 86 | 12.87 |
| Imputed as New Infection* | 0 | - | 30 | 4.13 | 0 | - |

Table 29: Details of the Classification of Patients by PCR-Corrected Cure Rates (ACPR) at Day 63 – AS+MQ (All Populations)

| Patient Classification | Pure-ITT (n = 381) | | m-ITT (n = 361) | | PP (n = 336) | |
|---|-----------------------|-------|--------------------|-------|-----------------|-------|
| | n | % | N | % | n | % |
| Recrudescence by PCR | 9 | 2.36 | 9 | 2.49 | 9 | 2.68 |
| Recrudescence due to informative withdrawal or failure before Day 3 | 23 | 6.04 | 3 | 0.83 | 1 | 0.30 |
| Imputed as Recrudescence* | 19 | 4.99 | 5 | 1.39 | 0 | - |
| New <i>P. falciparum</i> Infection by PCR | 38 | 9.97 | 38 | 10.53 | 38 | 11.31 |
| Malaria Infection \neq falciparum** | 65 | 17.06 | 65 | 18.01 | 65 | 19.35 |
| Imputed as New Infection* | 0 | - | 14 | 3.88 | 0 | - |

The minimum age was 6 months and very few children aged < 2 years were enrolled. The pure-ITT population results showed a decrease in PCR-corrected rates with increasing age (to < 90% for subjects aged 12 years or more) as shown below. In the m-ITT and PP populations, when stratified by age, there was no statistically significant difference in the PCR-corrected cure rates between treatments.

In the pure-ITT population shown below ($p = 0.022$) and in the m-ITT and PP populations ($p = 0.013$ for both) a statistically significant difference in the uncorrected cure rates was seen between treatments in the 18-65 year age group with higher rates for DHA/PQP and one-sided 97.5% CI above zero. This difference is stated to be due to more recrudescence infections and other plasmodial infections in the AS+MQ group than in the DHA/PQP group. In each population the uncorrected cure rates for both treatments in patients aged 18-65 years were lower than those seen in patients aged <18 years, suggesting that they had more new infections than patients aged <18 years.

Table 30: Summary of Cure Rates at Day 63 – by Age Classification (All Populations)

| Age Group (Years) | Cure Rate | DHA/PQP | | AS+MQ | | Treatment Difference (DHA/PQP - AS+MQ) | | | |
|-------------------|---------------|---------|-------|-------|-------|--|-----------------------------------|----------------------------|--------------------|
| | | n | % | n | % | Δ | Lower Limit of one-sided 97.5% CI | | Chi-square test, p |
| | | | | | | | Without Continuity Correction | With Continuity Correction | |
| Pure-ITT | | | | | | | | | |
| 0.5- 2 | PCR-corrected | 11 | 100 | 5 | 83.33 | 16.67 | -13.15 | -26.03 | 0.353 |
| | Uncorrected | 10 | 90.91 | 4 | 66.67 | 24.24 | -17.13 | -30.01 | 0.515 |
| 2 - 12 | PCR-corrected | 109 | 95.61 | 55 | 96.49 | -0.88 | -6.96 | -8.27 | 1 |
| | Uncorrected | 97 | 85.09 | 46 | 80.70 | 4.39 | -7.77 | -9.08 | 0.465 |
| 12 - 18 | PCR-corrected | 68 | 89.47 | 27 | 87.10 | 2.37 | -11.29 | -13.56 | 0.742 |
| | Uncorrected | 65 | 85.53 | 26 | 83.87 | 1.66 | -13.52 | -15.79 | 0.775 |
| 18 - 65 | PCR-corrected | 486 | 85.87 | 243 | 84.67 | 1.2 | -3.86 | -4.13 | 0.639 |
| | Uncorrected | 344 | 60.78 | 151 | 52.61 | 8.17 | 1.12 | 0.86 | 0.022 |

The difference between the PCR-corrected cure rates in Asian adults and adolescents vs. younger patients in the Pure ITT population (which was apparent in both treatment groups) were accounted for by the higher rates of LFU and missing PCR results. Subjects LFU and with missing PCR occurred more often in some countries and because of the different age ranges enrolled the effect appeared to be age-dependent when in fact it was a country-dependent effect. No significant effect of weight was detected.

There were differences between the uncorrected cure rates in adults vs. younger subjects in all analysis populations and such differences were apparent in both treatment groups. Within the DHA/PQP group these differences were not explained by age itself but by country and body weight.

- The applicant considered that the country effect could be explained by the variable transmission rates in different geographical areas.
- The applicant acknowledged that body weight appeared to have a role in predicting uncorrected cure rates that is independent of country but stressed that the differences by class of body weight still supported the efficacy of DHA/PQP vs. the comparator. On this basis the applicant considered that the data supported a dose adjustment according to body weight.

The PCR-corrected and uncorrected cure rates showed some variations between countries for each treatment. Within each country all rates were either comparable or slightly higher in the DHA/PQP group versus the AS+MQ group. The 97.5% one-sided CI for the difference (DHA/PQP-AS+MQ) in PCR-corrected cure rate adjusted by country was -0.84% in the m-ITT and -0.39% in the PP population.

Table 31: Summary of Cure Rates (ACPR) at Day 63 by Country (All Populations)

| Study Population | Cure Rate (%) | DHA/PQP | | | AS+MQ | | |
|------------------|---------------|---------|-------|----------|-------|-------|----------|
| | | India | Laos | Thailand | India | Laos | Thailand |
| Pure-ITT | PCR-corrected | 80.20 | 98.00 | 85.19 | 83.67 | 97.96 | 82.48 |
| | Uncorrected | 74.26 | 91.50 | 55.36 | 69.39 | 86.73 | 46.15 |
| m-ITT | PCR-corrected | 96.51 | 98.00 | 96.59 | 100 | 97.96 | 93.24 |
| | Uncorrected | 87.21 | 91.50 | 58.64 | 82.93 | 86.73 | 48.65 |
| PP | PCR-corrected | 98.75 | 99.48 | 98.24 | 100 | 98.92 | 95.54 |
| | Uncorrected | 91.25 | 93.19 | 63.73 | 82.93 | 87.10 | 53.47 |

Cure rates at Day 63 by country when non-interpretable, missing or not done PCRs were treated as either failures, successes or led to the exclusion of the corresponding patients showed the largest effect in Thailand. However, in each case the PCR-corrected and uncorrected cure rates for the m-ITT population were statistically homogeneous across countries and the 97.5% one-sided CI for the differences were within -5%.

In the Pure ITT population the overall PCR-corrected cure rates for DHA/PQP and for AS+MQ in India and Thailand were lower than corresponding rates for Laos. This was not observed in the other analysis populations. The applicant stated that the findings in the two treatment groups mainly reflected:

- LFU rates: no Laotian subject was LFU compared to 15% of Indian and 5% of Thai subjects (regardless of treatment group)
- Missing PCR results: 0-3% in India, 7-8% in Thailand vs. only one patient in Laos

The PCR-corrected cure rates for India appeared to decrease with age and body weight but weight was not found to be statistically significant in a logistic model based on the probability of cure that was applied to Pure ITT subjects in the DHA/PQP group.

The country-specific uncorrected cure rates appeared to decrease with increasing age in India and Thailand but there was little or no such effect in Laos. A trend for lower uncorrected cure rates with increasing weight was most apparent in India, was less consistent in Thailand and there was no clear trend in Laos. In a logistic model based on the probability to be cured in the DHA/PQP group the weight factor was found to be statistically significant in all analysis populations whereas the age factor was found to be statistically significant only in the Pure ITT population.

The proportions of patients with malaria due to other plasmodium species were similar between treatment groups. The proportions with new infections at Thai centres 12, 18 and 19 were lower than observed at all other centres, which suggested a lower malaria transmission rate although it should be noted that some new infections might have been missed because parasite density was not measured on Days 35, 49 or 56 at these three centres.

In addition, the uncorrected cure rates in the m-ITT and PP populations at centres 21 and 22 in Thailand were much lower than those seen at other centres. In the m-ITT population the uncorrected cure rates at centre 21 were 45.4% (DHA/PQP) vs. 31.3% (AS+MQ) and at centre 22 they were 43.7% (DHA/PQP) vs. 28.2% (AS+MQ) compared with 71.1% (DHA/PQP) and 62.9% (AS+MQ) for all centres. The results indicated that there were more new infections at centres 21 and 22 during the study compared with other centres including the other three Thai centres. Although patients at centres

12, 18 and 19 were treated in Bangkok, all Thai patients were recruited from the Thai-Burmese border region so it is unlikely that this difference was due to geographic location. Patients at centres 21 and 22 were only recruited to the second cohort and all were adults, so it was considered possible that seasonal variation in the malaria transmission rate, with a higher transmission during the second recruitment period, explained the lower uncorrected cure rates.

The early, late and true treatment failure rates at Day 63 were comparable between treatments in each population. The rates for the pure-ITT population are shown below.

Table 32: Summary of Early and Late Treatment Failure and True Treatment Failure Day 63 (Pure-ITT Population)

| Treatment Failure | DHA/PQP n = 767 | | AS+MQ n = 381 | | 95% CI on Difference (DHA/PQP - AS+MQ) |
|----------------------------|--------------------|-------|------------------|-------|---|
| | n | % | n | % | |
| Early & Late* | 105 | 13.69 | 58 | 15.22 | -5.88, 2.82% |
| Early (ETF) | 4 | 0.52 | 1 | 0.26 | -0.46, 0.98% |
| Late (LTF) | 101 | 13.17 | 57 | 14.96 | -6.10, 2.52% |
| Late Clinical (LCF) | 35 | 4.56 | 22 | 5.77 | -3.98, 1.56% |
| Late Parasitological (LPF) | 66 | 8.60 | 35 | 9.19 | -4.10, 2.93% |
| True** | 16 | 2.09 | 10 | 2.62 | -2.44, 1.36% |
| Early | 4 | 0.52 | 1 | 0.26 | -0.46, 0.98% |
| Late Recrudescence | 12 | 1.56 | 9 | 2.36 | -2.56, 0.96% |

At Day 28, there was a statistically significant difference between treatments (with lower rates for DHA/PQP) for the sum of ETF and LTF in the m-ITT population, which reflected the difference in LTF. Rates of ETF+LTF were also lower in the DHA/PQP group in the PP and pure-ITT populations. True TF rates were also lower with DHA/PQP and statistically significantly different in the PP population ($p = 0.003$). The 95% two-sided CIs for this comparison was (-3.49, -0.38%). The Day 42 findings showed the same pattern as at day 28.

There was no statistically significant difference between treatment groups in the proportion of aparasitaemic patients up to Day 3 in either the m-ITT or PP populations. The apparent fall in the proportion of aparasitaemic patients on Day 3 is because patients in Laos (approximately 25% of study population) did not have Day 3 assessments. The median time to parasite clearance (Kaplan-Meier estimate) was two days for DHA/PQP and AS+MQ in all three study populations.

Table 33: Proportion of Aparasitaemic Patients Days 1 – 3 (m-ITT and PP Populations)

| Day | DHA/PQP | | | | AS+MQ | | | |
|-----|---------|-------|-----|-------|-------|-------|-----|-------|
| | m-ITT | | PP | | m-ITT | | PP | |
| | n | % | n | % | n | % | n | % |
| 1 | 298 | 41.05 | 279 | 41.77 | 143 | 39.61 | 131 | 38.99 |
| 2 | 610 | 84.02 | 569 | 85.18 | 306 | 84.76 | 286 | 85.12 |
| 3 | 508 | 69.97 | 464 | 69.46 | 257 | 71.19 | 238 | 70.83 |

The apparent fall in the proportion of afebrile patients on Day 3 is also due to the lack of assessments in Laos. The median time to fever clearance could not be calculated because of too few assessments.

Table 34: Proportion of Afebrile Patients Days 0 – 3 (m-ITT and PP Populations)

| Day | DHA/PQP | | | | AS+MQ | | | |
|-----|---------|-------|-----|-------|-------|-------|-----|-------|
| | m-ITT | | PP | | m-ITT | | PP | |
| | n | % | n | % | n | % | n | % |
| 0 | 251 | 34.57 | 242 | 36.23 | 119 | 32.96 | 109 | 32.44 |
| 1 | 504 | 69.42 | 469 | 70.21 | 245 | 67.87 | 230 | 68.45 |
| 2 | 662 | 91.18 | 612 | 91.62 | 321 | 88.92 | 299 | 88.99 |
| 3 | 486 | 66.94 | 443 | 66.32 | 250 | 69.25 | 232 | 69.05 |

In the m-ITT population there was a statistically significant difference between treatments in fever rate on Day 1 (5.65% for DHA/PQP compared with 9.14% for AS+MQ; $p = 0.031$). However, there were 949/5039 person-fever-days in the DHA/PQP group compared with 478/2511 in the AS+MQ group.

Gametocytes were not assessed at Day 0. At Day 28 the proportion of patients with gametocytes was 1.24% (DHA/PQP) vs. 0% (AS+MQ) for the m-ITT and 1.05% vs. 0% (AS+MQ) for the PP population. Patients from centres 12, 18 and 19 did not have gametocytes assessed at Days 35, 49 and 56. Overall in the m-ITT population, gametocyte prevalence in the DHA/PQP group was 9.69% vs. 4.8% in the AS+MQ group. Person-gametocyte-weeks for the DHA/PQP group were five times that seen in the AS+MQ group (119/6276 person-weeks vs. 23/3052 person-weeks, which was statistically significant ($p = 0.026$)). Rates in the PP population were 101/5861 person-weeks vs. 23/2884 person weeks, which was not a statistically significant difference ($p = 0.064$). These data indicated that DHA/PQP has a lesser gametocytocidal effect than AS+MQ.

In the DHA/PQP group, the incidence of new infections was lower than seen in the AS+MQ group and the Kaplan-Meier curves showed that new infections tended to occur earlier after comparative treatment.

Table 35: New Infections at Day 63 (All Populations)

| Study Population | | DHA/PQP | | AS+MQ | |
|------------------|---|---------|-------|-------|-------|
| | | n | % | n | % |
| Pure-ITT | No. Patients Classified as New Infection by Day 63 | 158 | 20.60 | 103 | 27.03 |
| | No. Patients Censored | 609 | 79.40 | 278 | 72.97 |
| | Kaplan-Meier Estimate of the Proportion of Patients with New Infections at Day 63 | | 22.68 | | 30.33 |
| m-ITT | No. Patients Classified as New Infection by Day 63 | 188 | 25.90 | 117 | 32.41 |
| | No. Patients Censored | 538 | 74.10 | 244 | 67.59 |
| | Kaplan-Meier Estimate of the Proportion of Patients with New Infections at Day 63 | | 26.51 | | 33.72 |
| PP | No. Patients Classified as New Infection by Day 63 | 155 | 23.20 | 103 | 30.65 |
| | No. Patients Censored | 513 | 76.80 | 233 | 69.35 |
| | Kaplan-Meier Estimate of the Proportion of Patients with New Infections at Day 63 | | 23.40 | | 31.36 |

In the m-ITT and PP populations there was no significant difference between treatments in Hb change from baseline to either Days 28, 63 or to the last available data (LAD) using either the actual change in Hb or the last observation carried forward (LOCF) method.

In the pure-ITT population the mean Hb fell from 118.2 g/L (DHA/PQP) and 120 g/L (AS+MQ) on Day 0 to a nadir of 107.3 g/L (DHA/PQP) 109.9 g/L (AS+MQ) on Day 7, before increasing steadily thereafter. A similar trend was observed for Hct.

For the QC of PCR results the proportion of inconsistencies between the ITM laboratory and the independent expert (Professor G. Snounou) was 11/156 (7.1%). In addition, 35 samples were re-analysed by the SMRU laboratory and the proportion of inconsistencies between ITM and SMRU was 2/35 (5.7%), which was considered acceptable.

Results of the QC of parasitaemia slides at baseline and follow-up gave an estimated type 1 discrepancy rate (i.e. inversion of results among readers) between the site and the central laboratory of 12.7% (95% CI 10.7, 14.9), which was considered to be at the upper limit of acceptability. The high percentage of false positive results might have been due to deteriorating slide quality in the interval between the initial reading and the QC reading. The high percentage of false positive results in India might have led to an over-estimation of cure rates but the study report states that this would have been accounted for by the ITT analysis.

Ancillary analyses

After application of the WHO criteria (WHO, 2003) in order to compare the study results with the historical ones the Kaplan-Meier estimate of the true failure rates was less than 5% for both treatments. Therefore, the PCR-corrected cure rates defined by WHO (100 - true failure rate) for both treatments exceeded the 90% WHO threshold and the currently accepted 95% threshold on Days 63, 28 and 42. At Day 63 the PCR-corrected cure rates were 98.17% for DHA/PQP and 96.79% for AS+MQ.

Table 36: PCR-Corrected Cure Rates (ACPR) for Historical Comparisons (PP Population)

| Day | | DHA/PQP | | AS+MQ | |
|-----|--|---------|-------|-------|-------|
| | | n | % | N | % |
| 63 | Number of Patients Classified as Failures* | 11 | 1.65 | 10 | 2.98 |
| | Number Censored | 657 | 98.35 | 326 | 97.02 |
| | Kaplan-Meier Estimate of the Proportion of True Failures | | 1.83 | | 3.21 |
| 28 | Number of Patients Classified as Failures* | 1 | 0.15 | 7 | 2.08 |
| | Number Censored | 667 | 99.85 | 329 | 97.92 |
| | Kaplan-Meier Estimate of the Proportion of True Failures | | 0.15 | | 2.10 |
| 42 | Number of Patients Classified as Failures* | 5 | 0.75 | 8 | 2.38 |
| | Number Censored | 663 | 99.25 | 328 | 97.62 |
| | Kaplan-Meier Estimate of the Proportion of True Failures | | 0.77 | | 2.43 |

Study DM040011 (Africa study)

A phase III, randomised, non-inferiority trial to assess the efficacy and safety of Dihydroartemisinin + Piperaquine (DHA/PQP, Artekin™) in comparison with Artemether + Lumefantrine (A/L Coartem®) in children with uncomplicated *P. falciparum* malaria

Methods

This was a multi-centre, randomised, open label, two-arm parallel group study to determine whether DHA/PQP was non-inferior to Coartem (artemether-lumefantrine) and to assess its safety and tolerability in African children with acute uncomplicated *P. falciparum* malaria. DM 040011 was conducted between 16 August 2005 and 14 July 2006 at five study sites, one in each of five African countries

Study Participants

DM 040011 was to enrol subjects aged between 3 and 59 months of body weight ≥ 5 kg who had microscopically confirmed mono-infection with *P. falciparum* (parasitaemia 200 - 200,000/ μ L). They were also to have a history of fever or presence of fever (temperature $\geq 37.5^{\circ}\text{C}$). The general approach was as described for DM04010

Treatments

Subjects were randomised to DHA/PQP or comparator A/L (Coartem):

Coartem was manufactured by Novartis and only tablets containing artemether 20mg and lumefantrine 120mg were used. Dosing was as in the table followed immediately by a glass of milk.

Table 37

| Body Weight (kg) | Artemether Dose/Tablet (mg) | Lumefantrine Dose/Tablet (mg) | No. Tablets/Dose | No. Tablets/Day |
|------------------|-----------------------------|-------------------------------|------------------|-----------------|
| 5 to <15 | 20 | 120 | 1 | 2 |
| 15 to <25 | 40 | 240 | 2 | 4 |
| 25 to <35 | 60 | 360 | 3 | 6 |

The general approach to dosing was as in DM04010.

Objectives

The study aimed to demonstrate that the PCR-corrected cure rate of DHA/PQP was non-inferior to that of the comparator. This cure rate was defined as the proportion of patients with adequate clinical and parasitological response (ACPR) at Day 28 plus those treatment failures (TFs) identified as new *P. falciparum* (by PCR) and non-*falciparum* infections.

In order to compare the study results with the historical ones, the criteria described by WHO (2003) were used. These failure rates computed in each treatment group were judged against the efficacy threshold of 90% (WHO 2006). An efficacy threshold of <90%, obtained in an analysis carried out in accordance with the WHO requirements, indicates that a treatment should not be considered for first-line treatment policy.

Outcomes/endpoints

Thick and thin Giemsa stained blood smears were obtained to verify the presence of *P. falciparum* and to calculate asexual and sexual parasite density. The used methodology is as described for study DM040010.

The study aimed to demonstrate that the **PCR-corrected cure rate** of DHA/PQP was non-inferior to that of the comparator. This cure rate was defined as the proportion of patients with adequate clinical and parasitological response (ACPR) at **Day 28** plus those treatment failures (TFs) identified as new *P. falciparum* (by PCR) and non-*falciparum* infections.

ACPR was defined as absence of parasitaemia through to Day 28 irrespective of temperature and not meeting any of the criteria for early treatment failure (ETF) or late clinical (LCF) or parasitological failure (LPF). TF was defined as the sum of early and late TFs (ETF+LTF).

ETF was defined as:

1. Development of danger signs or severe malaria on Days 0, 1, 2 or 3, in the presence of parasitaemia.
2. Parasite density on Day 2 > Day 0 count, irrespective of temperature.
3. Presence of parasitaemia on Day 3 with fever (temperature $\geq 37.5^{\circ}\text{C}$).
4. Parasitaemia on Day 3 ≥ 25 % of count on Day 0.

LTF could be due to Late Clinical Failure (LCF) or Late Parasitological Failure (LPF):

LCF was defined as:

1. Development of danger signs or severe malaria after Day 3 in the presence of parasitaemia.
2. Presence of parasitaemia and fever on any day from Day 4 to Day 28, without previously meeting the criteria of ETF or LCF.

LPF was defined as reappearance of parasitaemia after initial clearance between Day 7 and Day 28 (identified as recrudescent infection by PCR analysis) in the absence of fever (temperature $<37.5^{\circ}\text{C}$) without previously meeting the criteria of ETF or LCF.

According to the protocol, efficacy analyses were to be performed on the pure Intention-To-Treat (pure-ITT; all treated), modified ITT (m-ITT; pure-ITT population with the exclusion of those patients lost-to-follow up for unknown reasons before Day 28) and the Per Protocol (PP; pure-ITT with no major protocol violations) populations. The m-ITT and the PP populations were the co-primary populations

Sample size

For DM 040011 the simulation concluded that if the PCR-corrected cure rate at Day 28 in the ITT population was in the range of 91 - 93% for A/L then a sample size of 500 patients in the A/L arm and 1000 patients in the DHA/PQP arm (1500 patients in total) was needed. A new formulation of the sample size requirement was part of the second protocol amendment. It was initially intended that each of the five sites would enrol 300 subjects to obtain the total of 1500 but this target was later increased to 500 for Mozambique due to under-enrolment in Kenya and Uganda in response to environmental conditions.

Randomisation

Subjects were randomised to DHA/PQP or comparator in a 2:1 ratio using sealed envelopes.

Blinding (masking)

An open label design was used because of the complexity of establishing a double-blind dosing schedule involving placebo tablets of DHA/PQP and placebo tablets of the comparator A/L.

All decisions pertaining to the allocation of patients to various analysis populations and the assessment of the primary endpoint were conducted in blinded conditions and without knowledge of the PCR results. The approach was as in DM04010.

Statistical methods

The lower limit of the one-sided 97.5% confidence interval (CI; = lower limit of the two-sided 95% CI) for the treatment difference in the percentage of PCR-corrected cure rates (ACPR) at Day 28 was computed. In order to confirm non-inferiority of DHA/PQP versus the comparator the CI lower limit was to be >-0.05 (i.e. within -5%) in both the m-ITT and the PP populations.

The PCR-corrected cure rates at Day 28 were to be described by country. The Breslow-Day test (if each country has at least two failures for each treatment) or logistic regression (otherwise) were to be used to evaluate homogeneity across countries. A similar approach was taken to analysis of outcomes by age groups.

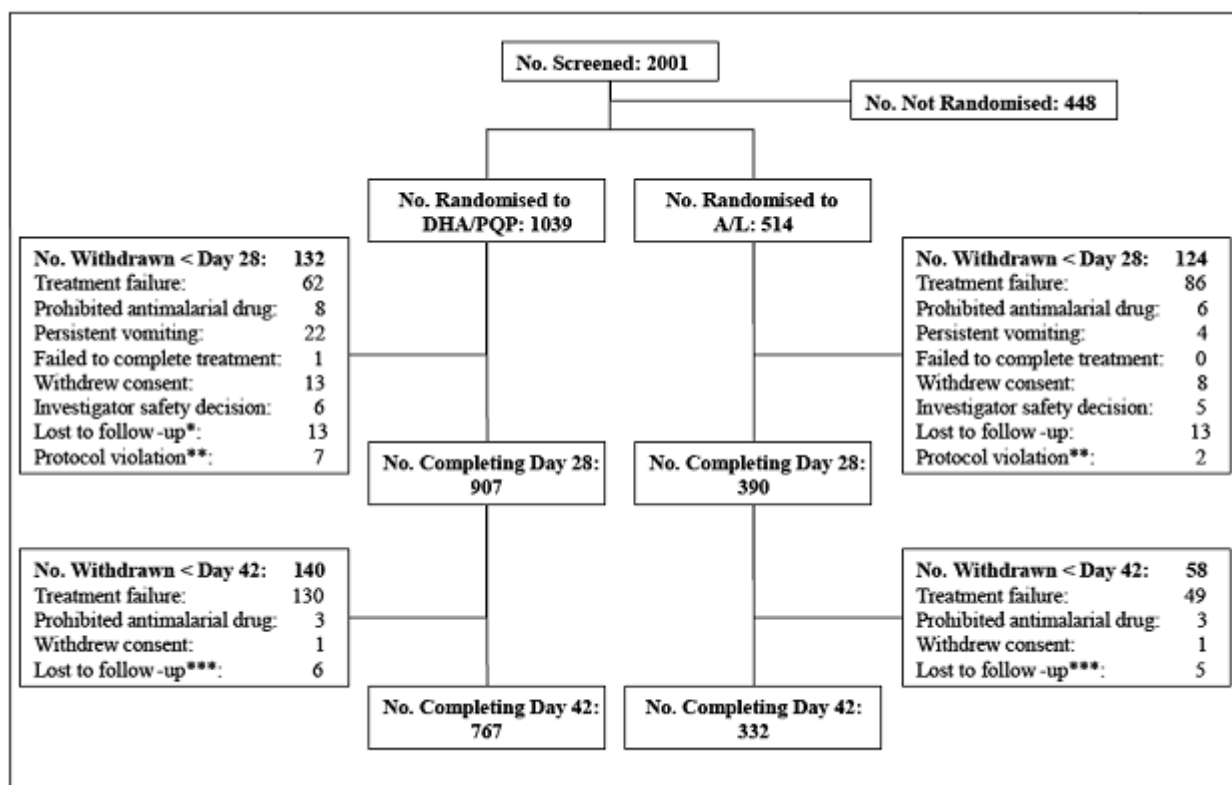
A range of sensitivity analyses was pre-defined. These included analyses in which:

- All patients with missing parasitaemia were treated as failures
- All patients with new infections as detected by PCR were excluded from the analysis (this analysis was added *post hoc*) following the suggestion of the study investigators.

Results

Participant flow

Figure 15: Patient Disposition



Of the 1039 patients randomised to DHA/PQP, 907 (87.3%) completed the study up to Day 28 compared to 390/514 (75.9%) patients randomised to A/L. Similarly, in the DHA/PQP group, 767 (73.8%) patients completed the study up to Day 42 compared to 332 (65%) in the A/L group. Completing the study meant that patients either reached a failure outcome or reached the last day of follow-up and the difference between treatments mainly reflected the failure rates

Recruitment

Five countries were involved in the African study, with 1 centre per country: Burkina Faso, Kenya, Mozambique, Uganda, and Zambia.

Table 38: Patient Accountability by Country – Study ST3073+ST3074 DM040011 (Safety/ITT Population)

| Country | DHA/PQP | | A/L | |
|---------------------|---------|-------|-----|-------|
| | n | % | n | % |
| Safety/ITT | 1038 | | 510 | |
| Burkina Faso | 201 | 19.36 | 100 | 19.61 |
| Kenya | 150 | 14.45 | 72 | 14.12 |
| Mozambique | 299 | 28.81 | 146 | 28.63 |
| Uganda | 185 | 17.82 | 91 | 17.84 |
| Zambia | 203 | 19.56 | 101 | 19.80 |

Conduct of the study

Changes in the conduct of the study included two general protocol amendments but only one of these occurred after enrolment had started. The amended protocol 21 June 2005 was issued on 15 November 2005 in response to the DMC who advised harmonising the statistical approaches for both studies in the Phase III programme. The changes were similar to those employed for study DM 040010 in the November 2005 amendment.

Baseline data

The minimum age enrolled was about 6 months in accordance with the protocol with mean and median ages of around 2.35 years. Some children in the DHA/PQP group were clearly older than the upper age limit in the protocol. Baseline parasite density was similar between treatment groups in all study populations but varied between countries, with the highest densities occurring in Kenya and Zambia and the lowest densities occurring in Burkina Faso. The overall range was 10,000 – 66,000 expressed per μL .

All patients had a history of fever which was of moderate severity in 81% in each treatment group. Fever was the only symptom that was considered severe (in 1.8% and 1% per group). Cough was the second most frequently reported symptom (45% per group). Mild weakness, anorexia, vomiting and flu symptoms were reported by >10% of patients in both treatment groups.

Data on medications taken before recruitment are likely unreliable but show that antipyretic drugs were by far the most frequent previous medications and mostly paracetamol was used. Fewer than 10% of patients had taken antimalarial drugs before recruitment.

Numbers analysed

The datasets analysed were as follows:

Table 39

| Data Set | DHA/PQP | | A/L | |
|-------------------|---------|-------|-----|-------|
| | n | % (*) | n | % (*) |
| Randomized | 1039 | | 514 | |
| Safety | 1038 | 99.90 | 510 | 99.22 |
| Pure-ITT | 1038 | 99.90 | 510 | 99.22 |
| m-ITT | 1027 | 98.85 | 497 | 96.69 |
| PP | 951 | 91.53 | 462 | 89.88 |

Outcomes and estimation

For the primary endpoint in the m-ITT and PP populations the PCR-corrected cure rates gave one-sided 97.5% CI for the difference DHA/PQP-A/L within -5%. This finding also applied in the pure-ITT population. For each treatment and population the uncorrected cure rates were lower than the PCR-corrected rates. In addition, the uncorrected cure rates were notably higher in each population for DHA/PQP and in each case the one-sided 97.5% CI exceeded zero.

Table 40: Summary of Cure Rates at Day 28 (All Populations)

| Study Population | Cure Rate | DHA/PQP | | A/L | | Treatment Difference (DHA/PQP - A/L) | | | |
|-----------------------------|---------------|---------|-------|-----|-------|--------------------------------------|-----------------------------------|----------------------------|--------------------|
| | | n | % | n | % | Δ | Lower Limit of one-sided 97.5% CI | | Chi-square test, p |
| | | | | | | | Without Continuity Correction | With Continuity Correction | |
| Pure-ITT (n = 1038, 510) | PCR-corrected | 938 | 90.37 | 459 | 90.00 | 0.37% | -2.80 % | -2.94% | 0.820 |
| | Uncorrected | 910 | 87.67 | 391 | 76.67 | 11.0% | 6.82 % | 6.68 % | <0.001 |
| m-ITT (n = 1027, 497) | PCR-corrected | 952 | 92.70 | 471 | 94.77 | -2.07% | -4.59 % | -4.74% | 0.128 |
| | Uncorrected | 910 | 88.61 | 391 | 78.67 | 9.94% | 5.84 % | 5.69 % | <0.001 |
| PP (n = 951, 462) | PCR-corrected | 910 | 95.69 | 442 | 95.67 | 0.02% | -2.24 % | -2.40 % | 0.988 |
| | Uncorrected | 884 | 92.95 | 376 | 81.39 | 11.56% | 7.67 % | 7.50 % | <0.001 |

The rate of recrudescence due to withdrawal or TF before Day 14 was slightly higher in the DHA/PQP group in both populations. The rate of new infections was much lower in the DHA/PQP group in both populations.

Table 41: Details of the Classification of Patients by PCR-Corrected Cure Rates (ACPR) at Day 28 – DHA/PQP (All Populations)

| Patient Classification | Pure-ITT (n = 1038) | | m-ITT (n = 1027) | | PP (n = 951) | |
|--|------------------------|------|---------------------|------|-----------------|------|
| | n | % | n | % | n | % |
| Recrudescence by PCR | 14 | 1.35 | 14 | 1.36 | 14 | 1.47 |
| Recrudescence due to informative withdrawal or failure before Day 14 | 65 | 6.26 | 54 | 5.26 | 27 | 2.84 |
| Imputed as Recrudescence* | 21 | 2.02 | 7 | 0.68 | 0 | - |
| New <i>P. falciparum</i> Infection by PCR | 28 | 2.70 | 28 | 2.73 | 26 | 2.73 |
| Malaria Infection \neq falciparum** | 1 | 0.10 | 1 | 0.10 | 1 | 0.11 |
| Imputed New Infection* | 0 | - | 14 | 1.36 | 0 | - |

Table 42: Details of the Classification of Patients by PCR-Corrected Cure Rates (ACPR) at Day 28 – A/L (All Populations)

| Patient Classification | Pure-ITT (n = 510) | | m-ITT (n = 497) | | PP (n = 462) | |
|--|-----------------------|-------|--------------------|-------|-----------------|-------|
| | n | % | n | % | N | % |
| Recrudescence by PCR | 11 | 2.16 | 11 | 2.21 | 11 | 2.38 |
| Recrudescence due to informative withdrawal or failure before Day 14 | 26 | 5.10 | 13 | 2.62 | 9 | 1.95 |
| Imputed as Recrudescence* | 14 | 2.75 | 2 | 0.40 | 0 | - |
| New <i>P. falciparum</i> Infection by PCR | 64 | 12.55 | 64 | 12.88 | 62 | 13.42 |
| Malaria Infection \neq falciparum** | 4 | 0.78 | 4 | 0.78 | 4 | 0.78 |
| Imputed New Infection* | 0 | - | 12 | 2.41 | 0 | - |

At Day 28, the proportions of true treatment failures were comparable between treatments. The sum of the ETFs and LTFs was lower for DHA/PQP than for A/L in all populations. This was mainly because of the difference in LTF rates between treatments.

The rates of ETFs were low but were higher in the DHA/PQP group. In the pure-ITT population 9/12 ETF patients in the DHA/PQP group and both patients in the A/L group were from Uganda and the most frequent reason for ETF was persistent vomiting at Day 0. Other reasons for ETF in the DHA/PQP group were a convulsion at Day 0, severe malaria on Day 0 requiring quinine and quinine given on Day 1 plus missing parasitaemia counts on Days 7 and 14.

Table 43: Summary of Early and Late Treatment Failure and True Treatment Failure at Day 28 (Pure-ITT Population)

| Treatment Failure | DHA/PQP n = 1038 | | A/L n = 510 | | 95% CI on Difference (DHA/PQP - A/L) |
|--------------------------------------|---------------------|------|----------------|-------|---|
| | n | % | n | % | |
| Early & Late* | 74 | 7.13 | 87 | 17.06 | -13.55, -6.31% |
| Early (ETF) | 12 | 1.16 | 2 | 0.39 | -0.08, 1.61% |
| Late (LTF) | 62 | 5.97 | 85 | 16.67 | -14.23, -7.15% |
| Late Clinical (LCF) | 7 | 0.67 | 26 | 5.10 | -6.40, -2.45% |
| Late Parasitological (LPF) | 55 | 5.30 | 59 | 11.57 | -9.36, -3.18% |
| True | 38 | 3.66 | 14 | 2.75 | -0.91, 2.74% |
| Early | 12 | 1.16 | 2 | 0.39 | -0.08, 1.61% |
| Late Treatment Failure before Day 14 | 11 | 1.06 | 1 | 0.20 | 0.13, 1.60% |
| Late Recrudescence | 15 | 1.45 | 11 | 2.16 | -2.17, 0.74% |

When stratified by age there was no difference between treatments in PCR-corrected cure rates in any study population but there was a statistically significant difference between treatments in uncorrected cure rates in the 12 - 24 and >24 month age groups in all study populations (the results for the pure-ITT population are shown below). In both these age sub-groups the uncorrected cure rate was higher in the DHA/PQP group. In contrast, there was no statistically significant difference between treatments in the uncorrected or PCR-corrected cure rates in children aged <12 months in any study population.

Table 44: Summary of Cure Rates at Day 28 by Age Classification (All Populations)

| Age Group (Months) | Cure Rate | DHA/PQP | | A/L | | Treatment Difference (DHA/PQP - A/L) | | | |
|--------------------|---------------|---------|-------|-----|-------|--------------------------------------|-----------------------------------|----------------------------|--------------------|
| | | n | % | n | % | Δ | Lower Limit of one-sided 97.5% CI | | Chi-square test, p |
| | | | | | | | Without Continuity Correction | With Continuity Correction | |
| Pure-ITT | | | | | | | | | |
| ≤12 | PCR-corrected | 117 | 90.70 | 63 | 92.65 | -1.95 | -9.92 | -11.05 | 0.643 |
| | Uncorrected | 117 | 90.70 | 60 | 88.24 | 2.46 | -6.69 | -7.81 | 0.586 |
| 12 - 24 | PCR-corrected | 268 | 89.04 | 139 | 90.85 | -1.81 | -7.59 | -8.08 | 0.549 |
| | Uncorrected | 260 | 86.38 | 116 | 75.82 | 10.56 | 2.75 | 2.26 | 0.005 |
| >24 | PCR-corrected | 553 | 90.95 | 257 | 88.93 | 2.02 | -2.25 | -2.50 | 0.338 |
| | Uncorrected | 553 | 87.66 | 215 | 74.39 | 13.27 | 7.60 | 7.34 | <0.001 |

The applicant stated that the expected rate of new infections is lower (and therefore the uncorrected cure rate is higher) in children aged ≤ 1 year due to some degree of shielding from mosquito bites as a result of close contact with the mother and maternal antibody (placental and milk-borne).

The 97.5% one-sided CI for the difference (DHA/PQP-A/L) in PCR-corrected cure rate adjusted by country was -4.56% in the m-ITT and -2.20% in the PP population. Cure rates were consistently lower for DHA/PQP versus A/L in Kenya (32). Removal of these data from the analysis did not notably affect the overall findings of the study.

Table 45: Summary of Cure Rates (ACPR) at Day 28 by Country (All Populations)

| Study Population | Cure Rate (%) | DHA/PQP | | | | | A/L | | | | |
|------------------|---------------|---------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | | 31 | 32 | 33 | 34 | 35 | 31 | 32 | 33 | 34 | 35 |
| Pure-ITT | PCR-corrected | 97.01 | 85.33 | 87.96 | 89.73 | 91.63 | 93.00 | 90.28 | 88.36 | 91.21 | 88.12 |
| | Uncorrected | 95.02 | 82.67 | 84.95 | 87.03 | 88.67 | 68.00 | 84.72 | 79.45 | 82.42 | 70.30 |
| m-ITT | PCR-corrected | 97.51 | 87.25 | 92.18 | 91.35 | 93.94 | 94.00 | 95.71 | 95.74 | 94.44 | 93.75 |
| | Uncorrected | 95.02 | 83.22 | 86.39 | 87.03 | 90.91 | 68.00 | 87.14 | 82.27 | 83.33 | 73.96 |
| PP | PCR-corrected | 98.48 | 93.13 | 93.07 | 99.36 | 95.31 | 94.85 | 96.92 | 96.92 | 96.25 | 93.33 |
| | Uncorrected | 96.46 | 90.08 | 90.15 | 96.79 | 92.19 | 69.07 | 92.31 | 86.92 | 86.25 | 74.44 |

The age and weight distributions of the children in Kenya versus the Other Countries (i.e. Mozambique, Burkina Faso, Zambia and Uganda) grouped together are provided in the next two tables for the Pure-ITT population.

Table 46: Patient Distribution by Age for Kenya and Other Countries (Pure-ITT Population)

| Class of Age (yrs) | Kenya | | | | Other Countries | | | |
|--------------------|-----------------|-------|------------|-------|-----------------|-------|-------------|-------|
| | DHA/PQP (N=150) | | A/L (N=72) | | DHA/PQP (N=888) | | A/L (N=438) | |
| ≤ 1 | 24 | 16.00 | 15 | 20.83 | 105 | 11.82 | 53 | 12.10 |
| (1-2] | 47 | 31.33 | 20 | 27.78 | 254 | 28.60 | 133 | 30.37 |
| (2-5] | 79 | 52.67 | 37 | 51.39 | 529 | 59.57 | 252 | 57.53 |

Table 47: Patient Distribution by Weight for Kenya and Other Countries (Pure-ITT Population)

| Class of Weight (kg) | Kenya | | | | Other Countries | | | |
|----------------------|-----------------|-------|------------|-------|-----------------|-------|-------------|-------|
| | DHA/PQP (N=150) | | A/L (N=72) | | DHA/PQP (N=888) | | A/L (N=438) | |
| < 7 | 2 | 1.33% | 1 | 1.39% | 17 | 1.91% | 6 | 1.37% |
| 7 to < 13 | 127 | 84.67 | 60 | 83.33 | 618 | 69.60 | 294 | 67.12 |
| 13 to < 24 | 21 | 14.00 | 11 | 15.28 | 252 | 28.38 | 138 | 31.51 |
| 24 to < 36 | 0 | | 0 | | 1 | 0.11% | 0 | |

In Kenya and in Other Countries the majority of patients were aged from 2 to ≤ 5 years and weighed from 7 to < 13 kg. Age and weight distributions were comparable between treatment groups within Kenya and within the Other Countries. However in Kenya more patients assigned to DHA/PQP were aged ≤ 2 years with respect to the Other Countries (47.3% vs. 40.4%) and, in parallel with the shift in age distribution, more fell into the weight band ≥ 7 to < 13 kg (84.7% vs. 69.6%). The same pattern of differences in age and weight distributions between Kenyan and other children applied in the A/L group.

The Cure Rates at Days 28 and 42 in Kenya and Other Countries were provided by age group and overall and by class of body weight and overall. The PCR-corrected cure rates at D28 and D42 among the Kenyan DHA/PQP patients did not show a trend to vary with age or weight. The applicant considers that the apparent variation in the size of the treatment differences across the classes of age and weight was due to fluctuation of results in the A/L group, which was considered to be random in nature. The same conclusion was drawn with regard to the uncorrected cure rates. Since age and weight did not seem to explain the lower cure rates observed with DHA/PQP in Kenya the applicant explored other factors (e.g. parasite density at baseline) that might contribute to the finding but was not able to identify any clear explanation. The applicant considers that the finding occurred by chance among the relatively low numbers enrolled in Kenya.

Treating m-ITT patients with non-interpretable, missing or not done PCRs as either failures, successes or excluding them had no statistically significant effect on the PCR-corrected cure rates and the 97.5% one-sided CI was within 5% in all instances. However, all three approaches gave a highly statistically significant effect on the uncorrected cure rate that reflected the data from Burkina Faso and Zambia where the greatest difference between treatments in uncorrected cure rates was observed.

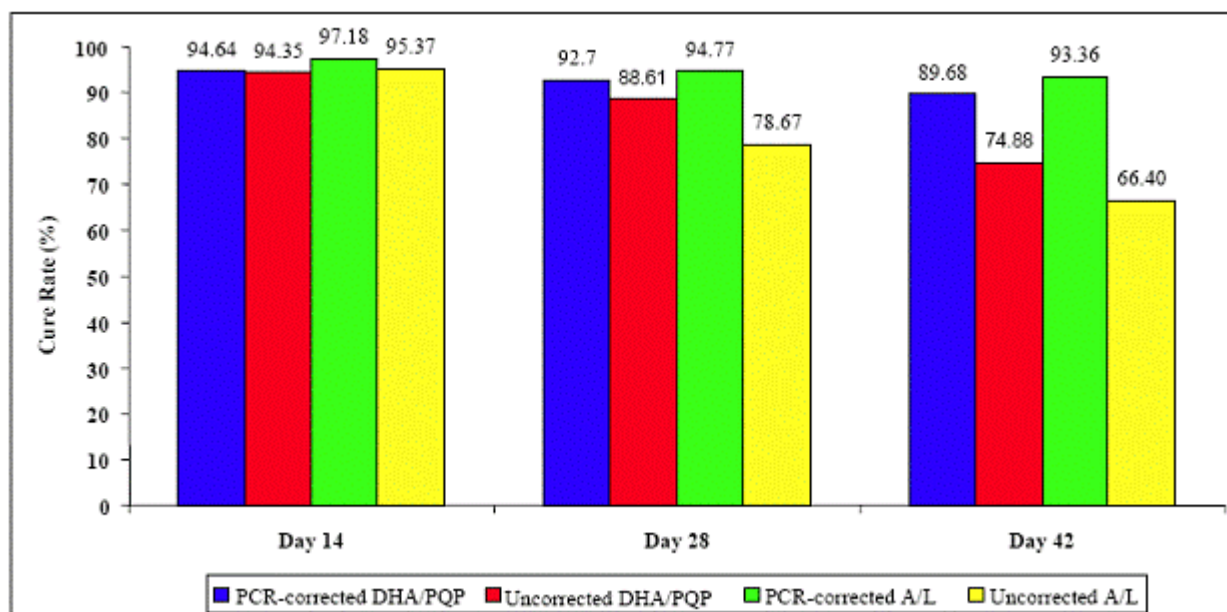
The results of the pre-planned input strategies for patients who were lost-to-follow-up and for patients without a valid PCR result (pure-ITT population) gave PCR-corrected cure rates that ranged from 90.94 - 93.43% for the DHA/PQP group and 91.27 - 94.90% for the A/L group. For all strategies, the 97.5% one-sided CI was within -5%. When all patients with missing parasitaemia data were classified as failures the 97.5% one-sided CI remained within -5%. Excluding patients with new *P. falciparum* infection detected by PCR or new non-*falciparum* infection had minimal effects on the PCR-corrected cure rates and the 97.5% one-sided CI remained within -5% in all populations.

At Day 14 in both the m-ITT and the PP populations the lower limits of the two-sided 95% CI for PCR-corrected cure rates were within -5%. There were no statistically significant differences in uncorrected cure rates between treatments and these resembled their corresponding PCR-corrected rates. At Day 42 the PCR-corrected cure rates in the m-ITT and PP populations were slightly higher in the A/L group. The lower limits of the two-sided 95% CIs were within -5% in the pure-ITT and the PP populations but the limit was -6.55 in the m-ITT population. However, the treatment differences in uncorrected cure rates were significant in all study populations in favour of the DHA/PQP group.

In the m-ITT population the rates of recrudescence at Day 42 were generally comparable between treatments. The statistically significant difference ($p < 0.001$) in uncorrected cure rates (ACPR) between treatments reflected the lower rates of new *P. falciparum* or non-*falciparum* infections by Day 42 for DHA/PQP compared to A/L with rates of 11.9% vs. 21.1% in the m-ITT population and 12.4% vs. 22.1% in the PP population.

By Day 42, the sum of ETFs and LTFs for DHA/PQP was lower than for A/L at 19.8% vs. 27.8% ($p < 0.001$) in the m-ITT population and 18.7% vs. 26.4% ($p < 0.001$) in the PP population. This was due to fewer LTFs (LCF and LPF) in the DHA/PQP group. The late treatment failure rates were 18.6% vs. 27.4% ($p < 0.001$) in the m-ITT and 18.6% vs. 26.4% ($p < 0.001$) in the PP population for respective treatments. The true treatment failure rates were 6.3% vs. 4% in the m-ITT and 5.6% vs. 3.7% in the PP population.

Figure 16: PCR-Corrected and Uncorrected Cure Rates at Days 14, 28 and 42 (m-ITT Population)



In each of the m-ITT and PP populations higher proportions of patients in the DHA/PQP group were aparasitaemic on Day 1 (24 h after starting treatment). The median time to parasite clearance (Kaplan-Meier estimate) was two days for both treatments in all three study populations.

Table 48: Proportion of Aparasitaemic Patients Days 0 – 3 (m-ITT and PP Populations)

| Day | DHA/PQP | | | | A/L | | | |
|-----|---------|-------|-----|-------|-------|-------|-----|-------|
| | m-ITT | | PP | | m-ITT | | PP | |
| | n | % | n | % | n | % | n | % |
| 0 | 1 | 0.10 | 0 | - | 1 | 0.20 | 0 | - |
| 1 | 370 | 36.03 | 351 | 36.91 | 142 | 28.57 | 133 | 28.79 |
| 2 | 863 | 84.03 | 815 | 85.70 | 420 | 84.51 | 392 | 84.85 |
| 3 | 1003 | 97.66 | 939 | 98.74 | 489 | 98.39 | 457 | 98.92 |

Slightly higher proportions in the DHA/PQP group were afebrile at Day 1. Three measurements over a 48 h period were too few to allow calculation of the median time to fever clearance.

Table 49: Proportion of Afebrile Patients Days 0 – 3 (m-ITT and PP Populations)

| Day | DHA/PQP | | | | A/L | | | |
|-----|---------|-------|-----|-------|-------|-------|-----|-------|
| | m-ITT | | PP | | m-ITT | | PP | |
| | n | % | n | % | n | % | n | % |
| 0 | 413 | 40.21 | 388 | 40.80 | 200 | 40.24 | 185 | 40.04 |
| 1 | 919 | 89.48 | 855 | 89.91 | 421 | 84.71 | 394 | 85.28 |
| 2 | 1001 | 97.47 | 935 | 98.32 | 483 | 97.18 | 451 | 97.62 |
| 3 | 1000 | 97.37 | 934 | 98.21 | 491 | 98.79 | 459 | 99.35 |

While comparable proportions (11-13%) in the treatment groups and populations had gametocytes at enrolment a higher proportion in the DHA/PQP group still had gametocytes at Day 2 (16.7% vs. 9.3% in the m-ITT population). This difference persisted and was statistically significant until Day 21 in both study populations indicating that DHA/PQP had a lesser gametocytocidal effect than A/L.

There was no significant differences between treatments in Hb change from baseline to either Day 28 or Day 42 but changes to last available data (LAD) were statistically significantly different between treatments (17.3 g/L DHA/PQP vs. 14.8 g/L A/L, ANOVA, $p = 0.016$ m-ITT and similar results for the PP population), which may reflect the higher number of new *P. falciparum* infections by PCR and new non-*falciparum* infections and thus associated anaemia occurring in the A/L-treated patients.

Quality control of PCR analyses showed that the proportion of inconsistencies between the ITM laboratory and the independent expert (Professor G. Snounou) was 37/317 (11.7%). The rate of inconsistencies between the ITM and the SMRU laboratories was 2/58 (3.4%), which was considered acceptable. The level of agreement between the independent observers was adequate.

Quality control of parasitaemia slides at baseline and follow-up gave an estimated percentage of type I discrepancies (i.e. inversion of results among readers) between the site and the central laboratory readings of 7.6% (95% CI 5.9, 9.8), which was similar to that reported in the literature. Kenya did not participate in this exercise.

Ancillary analyses

After applying the WHO criteria (WHO, 2003) the Kaplan-Meier estimate of the true failure rates at Day 28 was 2.77 for both treatments. Therefore, the PCR-corrected cure rates defined by WHO (100- true failure rate) of both treatments were equal to 97.23% and exceeded both the 90% WHO threshold and 95% threshold for new treatments. The study report states that the performance of A/L in the present study was consistent with that expected from the literature. For example, true failure rates in the PP populations at day 28 of 1.9%, 3.2 % and 2.7% were reported in different studies. Higher rates were reported in two publications: (7.0%; von Seidlein L *et al* 1997 and 8.9%; Kanya MR *et al* 2007) but both of these studies were conducted in areas and seasons with a particularly high transmission rate.

Table 50: PCR-Corrected Cure Rates (ACPR) at Day 28 for Historical Comparisons (PP Population)

| | DHA/PQP | | A/L | |
|--|---------|-------|-----|-------|
| | n | % | n | % |
| No. Patients Classified as Failures* | 26 | 2.73 | 12 | 2.60 |
| No. Censored | 925 | 97.27 | 450 | 97.40 |
| Kaplan-Meier Estimate of the Proportion of True Failures at Day 28 | | 2.77 | | 2.77 |

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 51: Table Summary of Efficacy for trial DM040010

| | | | |
|---|---|---|--|
| Title: A Phase III, Randomised, Non-Inferiority Trial, to Assess the Efficacy and Safety of Dihydroartemisinin/Piperaquine (DHA/PQP, Artekin™) in Comparison with Artesunate + Mefloquine (AS+MQ) in Patients Affected by Acute, Uncomplicated <i>P.falciparum</i> Malaria | | | |
| Study identifier | ST3073+ST3074-DM040010 | | |
| Design | multi-centre, phase III, randomised, open label, two-arm parallel group study | | |
| | Duration of main phase: | | 63 days (planned) |
| | Duration of run-in phase: | | not applicable |
| | Duration of extension phase: | | not applicable |
| Hypothesis | Non-inferiority | | |
| Treatment groups | DHA/PQP | | Dihydroartemisinin/Piperaquine. 3 days, 769 |
| | AS+MQ | | Artesunate+Mefloquine. 3 days, 381 |
| Endpoints and definitions | Co-primary endpoints | COR-MITT-D63 COR-PP-D63 | Day 63 PCR-corrected cure rates in modified-ITT and Per Protocol populations |
| | Secondary endpoints | S1: COR-<POP>-<DAY> | PCR-corrected cure rates at Days 28 and 42 in all populations |
| | | S2: UNC-<POP>-<DAY> | Uncorrected cure rates at Days 28, 42 and 63 in all populations |
| | | S3 | Proportion of patients with treatment failure |
| | | S4 | Proportion of aparasitaemic patients and time to parasitaemia clearance |
| | | S5 | Proportion of afebrile patients and time to fever clearance |
| | | S6 | Proportion of patients with gametocytes at various time points |
| | | S7 | Haematological recovery |
| | | S8 | Compliance with study treatment |

| | | | |
|--|---|---|-----------------|
| | | Note: <POP>=MITT (Modified-ITT), PP (Per Protocol), ITT (Pure ITT/Safety); <DAY>=28, 42, 63 | |
| Database lock | 06 November 2007 | | |
| Results and analysis | | | |
| Analysis description | Primary analysis: COR-MITT-D63 and COR-PP-D63 | | |
| Analysis population and time point description | Modified-ITT Population Day 63 | | |
| Descriptive statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | COR-MITT-D63 (N (%)) | 704 (96.97%) | 344 (95.29%) |
| Effect estimate per comparison | Primary endpoint | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | -0.84% |
| | | P-value | 0.161 |
| Notes | CI LL = Confidence Interval Lower Limit | | |
| Analysis population and time point description | Per Protocol Population Day 63 | | |
| Descriptive statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | COR-PP-D63 (N (%)) | 659 (98.65%) | 326 (97.02%) |
| Effect estimate per comparison | Primary endpoint | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | -0.39% |
| | | P-value | 0.074 |
| Notes | CI LL = Confidence Interval Lower Limit | | |
| Analysis description | Secondary analysis S1: COR-MITT-D28, COR-MITT-D42, COR-PP-D28, COR-PP-D42, COR-ITT-D28, COR-ITT-D42, COR-ITT-D63 | | |
| Analysis population and time point description | Modified-ITT Population Day 28 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | COR-MITT-D28 (N (%)) | 715 (98.48%) | 348 (96.40%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | -0.03% |
| | | P-value | 0.028 |
| Analysis population and time point description | Modified-ITT Population Day 42 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |

| | | | |
|--|-----------------------------------|-----------------------|-----------------|
| | COR-MITT-D42 (N (%)) | 709 (97.66%) | 346 (95.84%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | -0.52% |
| | | P-value | 0.096 |
| Analysis population and time point description | Per Protocol Population Day 28 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | COR-PP-D28 (N (%)) | 667 (99.85%) | 329 (97.92%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 0.38% |
| | | P-value | 0.001 |
| Analysis population and time point description | Per Protocol Population Day 42 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | COR-PP-D42 (N (%)) | 663 (99.25%) | 328 (97.62%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | -0.12% |
| | | P-value | 0.031 |
| Analysis population and time point description | Pure ITT Population Day 28 | | |
| Descriptive statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | COR-ITT-D28 (N (%)) | 719 (93.74%) | 350 (91.86%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | -1.36% |
| | | P-value | 0.236 |
| Analysis population and time point description | Pure ITT Population Day 42 | | |
| Descriptive statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | COR-ITT-D42 (N (%)) | 694 (90.48%) | 336 (88.19%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | -1.56% |
| | | P-value | 0.228 |
| Analysis population and time point description | Pure ITT Population Day 63 | | |

| | | | |
|--|--|-----------------------|-----------------|
| Descriptive statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | COR-ITT-D63 (N (%)) | 674 (87.87%) | 330 (86.61%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | -2.87% |
| | | P-value | 0.544 |
| Notes | CI LL = Confidence Interval Lower Limit | | |
| Analysis description | Secondary analysis S2: UNC-MITT-D28, UNC-MITT-D42, UNC-MITT-D63 UNC-PP-D28, UNC-PP-D42, UNC-PP-D63 UNC-ITT-D28, UNC-ITT-D42, UNC -ITT-D63 | | |
| Analysis population and time point description | Modified-ITT Population Day 28 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | UNC-MITT-D28 (N (%)) | 693 (95.45%) | 328 (90.86%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 1.26% |
| | | P-value | 0.003 |
| Analysis population and time point description | Modified-ITT Population Day 42 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | UNC-MITT-D42 (N (%)) | 630 (86.78%) | 291 (80.61%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 1.40% |
| | | P-value | 0.008 |
| Analysis population and time point description | Modified-ITT Population Day 63 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | UNC-MITT-D63 (N (%)) | 516 (71.07%) | 227 (62.88%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 2.22% |
| | | P-value | 0.006 |
| Analysis population and time point description | Per Protocol Population Day 28 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |

| | | | |
|--|-----------------------------------|-----------------------|-----------------|
| | UNC-PP-D28 (N (%)) | 656 (98.20%) | 315 (93.75%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 1.68% |
| | | P-value | <0.001 |
| Analysis population and time point description | Per Protocol Population Day 42 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | UNC-PP-D42 (N (%)) | 609 (91.17%) | 287 (85.42%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 1.41% |
| | | P-value | 0.006 |
| Analysis population and time point description | Per Protocol Population Day 63 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | UNC-PP-D63 (N (%)) | 504 (75.45%) | 223 (66.37%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 3.07% |
| | | P-value | 0.002 |
| Analysis population and time point description | Pure ITT Population Day 28 | | |
| Descriptive statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | UNC-ITT-D28 (N (%)) | 708 (92.31%) | 336 (88.19%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 0.37% |
| | | P-value | 0.022 |
| Analysis population and time point description | Pure ITT Population Day 42 | | |
| Descriptive statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | UNC-ITT-D42 (N (%)) | 638 (83.18%) | 295 (77.43%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 0.79% |
| | | P-value | 0.019 |
| Analysis population and time point description | Pure ITT Population Day 63 | | |

| | | | |
|--|---|-----------------------|------------------|
| Descriptive statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | UNC-ITT-D63 (N (%)) | 516 (67.28%) | 227 (59.58%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – AS+MQ |
| | | 97.5% one-sided CI LL | 1.75% |
| | | P-value | 0.010 |
| Notes | CI LL = Confidence Interval Lower Limit | | |
| Analysis description | Secondary analysis S3: Early, Late and True Treatment Failures (ETF, LTF and True) | | |
| Analysis population and time point description | Pure ITT Population Day 63 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | ETF (N (%)) | 4 (0.52%) | 1 (0.26%) |
| | LTF (N (%)) | 101 (13.17%) | 57 (14.96%) |
| | ETF+LTF (N (%)) | 105 (13.69%) | 58 (15.22%) |
| | True (N (%)) | 16 (2.09%) | 10 (2.62%) |
| Effect estimate per comparison | ETF+LTF | Comparison groups | DHA/PQP – AS+MQ |
| | | 95% CI | (-5.88% ; 2.82%) |
| | | P-value | 0.483 |
| | True | Comparison groups | DHA/PQP – AS+MQ |
| | | 95% CI | (-2.44% ; 1.36%) |
| | | P-value | 0.564 |
| Analysis population and time point description | Modified-ITT Population Day 63 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | ETF (N (%)) | 4 (0.55%) | 1 (0.28%) |
| | LTF (N (%)) | 101 (13.91%) | 57 (15.79%) |
| | ETF+LTF (N (%)) | 105 (14.46%) | 58 (16.07%) |
| | True (N (%)) | 16 (2.20%) | 10 (2.77%) |
| Effect estimate per comparison | ETF+LTF | Comparison groups | DHA/PQP – AS+MQ |
| | | 95% CI | (-6.17% ; 2.97%) |
| | | P-value | 0.486 |
| | True | Comparison groups | DHA/PQP – AS+MQ |
| | | 95% CI | (-2.57% ; 1.44%) |
| | | P-value | 0.565 |
| Analysis population and time point description | Per Protocol Population Day 63 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | ETF (N (%)) | 0 | 1 (0.30%) |
| | LTF (N (%)) | 86 (12.87%) | 52 (15.48%) |

| | | | |
|--|--|-------------------|------------------|
| | ETF+LTF (N (%)) | 86 (12.87%) | 53 (15.77%) |
| | True (N (%)) | 11 (1.65%) | 10 (2.98%) |
| Effect estimate per comparison | ETF+LTF | Comparison groups | DHA/PQP – AS+MQ |
| | | 95% CI | (-7.55% ; 1.75%) |
| | | P-value | 0.209 |
| | True | Comparison groups | DHA/PQP – AS+MQ |
| | | 95% CI | (-3.39% ; 0.73%) |
| | | P-value | 0.165 |
| Analysis description | Secondary analysis S4: Aparasitaemic patients and time to parasitaemia clearance | | |
| Analysis population and time point description | Modified-ITT Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | Aparasitaemic at Day 0 (N (%)) | 0 | 0 |
| | Aparasitaemic at Day 1 (N (%)) | 298 (41.05%) | 143 (39.61%) |
| | Aparasitaemic at Day 2 (N (%)) | 610 (84.02%) | 306 (84.76%) |
| | Aparasitaemic at Day 3 (N (%)) | 508 (69.97%) | 257 (71.19%) |
| Kaplan-Meier estimate | Median time to parasitaemia clearance (days) | 2 | 2 |
| Analysis population and time point description | Per Protocol Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | Aparasitaemic at Day 0 (N (%)) | 0 | 0 |
| | Aparasitaemic at Day 1 (N (%)) | 279 (41.77%) | 131 (38.99%) |
| | Aparasitaemic at Day 2 (N (%)) | 569 (85.18%) | 286 (85.12%) |
| | Aparasitaemic at Day 3 (N (%)) | 464 (69.46%) | 238 (70.83%) |
| Kaplan-Meier estimate | Median time to parasitaemia clearance (days) | 2 | 2 |
| Analysis description | Secondary analysis S5: Afebrile patients and time to fever clearance | | |
| Analysis population and time point description | Modified-ITT Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |

| | | | |
|---|--|-------------------|-------------------|
| | Afebrile at Day 0 (N (%)) | 251 (34.57%) | 119 (32.96%) |
| | Afebrile at Day 1 (N (%)) | 504 (69.42%) | 245 (67.87%) |
| | Afebrile at Day 2 (N (%)) | 662 (91.18%) | 321 (88.92%) |
| | Afebrile at Day 3 (N (%)) | 486 (66.94%) | 250 (69.25%) |
| Kaplan-Meier estimate | Median time to fever clearance (days) | Not available (*) | Not available (*) |
| Notes | (*) It could not be calculated because of too few assessment timepoints | | |
| Analysis population and time point description | Per Protocol Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | Afebrile at Day 0 (N (%)) | 242 (36.23%) | 109 (32.44%) |
| | Afebrile at Day 1 (N (%)) | 469 (70.21%) | 230 (68.45%) |
| | Afebrile at Day 2 (N (%)) | 612 (91.62%) | 299 (88.99%) |
| | Afebrile at Day 3 (N (%)) | 443 (66.32%) | 232 (69.05%) |
| Kaplan-Meier estimate | Median time to fever clearance (days) | Not available (*) | Not available (*) |
| Notes | (*) It could not be calculated because of too few assessment timepoints | | |
| Analysis description | Secondary analysis S6: Patients with gametocytes at various timepoints | | |
| Analysis population and time point description | Modified-ITT Population | | |
| Descriptive Statistics Number of patients with gametocytes (N (%)) | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | Day 7 | 52 (7.16%) | 14 (3.88%) |
| | Day 14 | 28 (3.86%) | 3 (0.83%) |
| | Day 21 | 12 (1.65%) | 0 |
| | Day 28 | 9 (1.24 %) | 0 |
| Notes | Gametocytes were not assessed at Day 0 | | |
| Analysis population and time point description | Per Protocol Population | | |
| Descriptive Statistics Number of patients with gametocytes (N (%)) | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | Day 7 | 48 (7.19%) | 14 (4.17%) |
| | Day 14 | 25 (3.74%) | 3 (0.89%) |
| | Day 21 | 10 (1.50%) | 0 |

| | | | |
|---|--|----------------|----------------|
| | Day 28 | 7 (1.05 %) | 0 |
| Notes | Gametocytes were not assessed at Day 0 | | |
| Analysis description | Secondary analysis S7: Haematological Recovery | | |
| Analysis population and time point description | Safety/Pure ITT Population | | |
| Descriptive Statistics Hb Fractional (g/L) mean (std) | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | Day 0 (*) | 118.17 (24.46) | 119.98 (23.22) |
| | Nadir (Day 7) | 107.26 (21.30) | 109.87 (21.97) |
| | Day 28 | 121.63 (16.47) | 122.72 (17.77) |
| Notes | (*) Day 0 values are taken from Table 12.4.1.2a of FSR, which is for Hb in the whole sample, while values for the other days have been taken from Table 12.4.1.2b which is for Hb Fractional in a subset of patients (~28% of the whole sample) | | |
| Analysis description | Secondary analysis S8: Compliance with study treatment: Patients having taken at least 80% of the scheduled study treatment | | |
| Analysis population and time point description | Safety/Pure ITT Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 767 | 381 |
| | Compliance ≥80% | 764 (99.61%) | 379 (99.48%) |
| Analysis population and time point description | Modified-ITT Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 726 | 361 |
| | Compliance ≥80% | 723 (99.59%) | 359 (99.45%) |
| Analysis population and time point description | Per Protocol Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | AS+MQ |
| | Number of subjects | 668 | 336 |
| | Compliance ≥80% | 668 (100%) | 336 (100%) |

Table 52: Table Summary of Efficacy for trial DM040011

| | | |
|--|---|-------------------|
| Title: A Phase III, Randomised, Non-Inferiority Trial, to Assess the Efficacy and Safety of Dihydroartemisinin + Piperaquine (DHA/PQP, Artekin™) in Comparison with Artemether + Lumefantrine (A/L, Coartem®) in Children with Uncomplicated <i>P. falciparum</i> Malaria | | |
| Study identifier | ST3073+ST3074-DM040011 | |
| Design | multi-centre, phase III, randomised, open label, two-arm parallel group study | |
| | Duration of main phase: | 42 days (planned) |
| | Duration of run-in phase: | not applicable |
| | Duration of extension phase: | not applicable |

| | | | |
|--|---|---|--|
| Hypothesis | Non-inferiority | | |
| Treatment groups | DHA/PQP | | Dihydroartemisinin/Piperaquine. 3 days, 1039 |
| | A/L | | Artemether/lumefantrine. 3 days, 514 |
| Endpoints and definitions | Co-primary endpoints | COR-MITT-D28 COR-PP-D28 | Day 28 PCR-corrected cure rates in modified-ITT and Per Protocol populations |
| | Secondary endpoints | S1: COR-<POP>-<DAY> | PCR-corrected cure rates at Days 14 and 42 in all populations |
| | | S2: UNC-<POP>-<DAY> | Uncorrected cure rates at Days 14, 28 and 42 in all populations |
| | | S3 | Proportion of patients with treatment failure |
| | | S4 | Proportion of aparasitaemic patients and time to parasitaemia clearance |
| | | S5 | Proportion of afebrile patients and time to fever clearance |
| | | S6 | Proportion of patients with gametocytes at various time points |
| | | S7 | Fractional change in haemoglobin/haematocrit (Hb/Hct) |
| | | S8 | Compliance with study treatment |
| | | Note: <POP>=MITT (Modified-ITT), PP (Per Protocol), ITT=Pure ITT/Safety. <DAY>=14, 28, 42 | |
| Database lock | 18 April 2007 | | |
| Results and analysis | | | |
| Analysis description | Primary analysis: COR-MITT-D28 and COR-PP-D28 | | |
| Analysis population and time point description | Modified-ITT Population Day 28 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | COR-MITT-D28 (N (%)) | 952 (92.70%) | 471 (94.77%) |
| Effect estimate per comparison | Primary endpoint | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -4.59% |
| | | P-value | 0.128 |
| Notes | CI LL = Confidence Interval Lower Limit | | |
| Analysis population and time point description | Per Protocol Population Day 28 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | COR-PP-D28 (N (%)) | 910 (95.69%) | 442 (95.67%) |
| Effect estimate per comparison | Primary endpoint | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -2.24% |
| | | P-value | 0.988 |

| | | | |
|--|---|-----------------------|---------------|
| Notes | CI LL = Confidence Interval Lower Limit | | |
| Analysis description | Secondary analysis S1: COR-MITT-D14, COR-MITT-D42, COR-PP-D14, COR-PP-D42, COR-ITT-D14, COR-ITT-D28, COR-ITT-D42 | | |
| Analysis population and time point description | Modified-ITT Population Day 14 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | COR-MITT-D14 (N (%)) | 972 (94.64%) | 483 (97.18%) |
| Effect estimate per comparison | Primary endpoint | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -4.54% |
| | | P-value | 0.025 |
| Analysis population and time point description | Modified-ITT Population Day 42 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | COR-MITT-D42 (N (%)) | 921 (89.68%) | 464 (93.36%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -6.55% |
| | | P-value | 0.019 |
| Analysis population and time point description | Per Protocol Population Day 14 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | COR-PP-D14 (N (%)) | 924 (97.16%) | 453 (98.05%) |
| Effect estimate per comparison | Primary endpoint | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -2.53% |
| | | P-value | 0.319 |
| Analysis population and time point description | Per Protocol Population Day 42 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | COR-PP-D42 (N (%)) | 879 (92.43%) | 436 (94.37%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -4.63% |
| | | P-value | 0.177 |
| Analysis population and time point description | Pure ITT Population Day 14 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |

| | | | |
|--|--|-----------------------|---------------|
| | Number of subjects | 1038 | 510 |
| | COR-ITT-D14 (N (%)) | 975 (93.93%) | 486 (95.29%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -3.71% |
| | | P-value | 0.274 |
| Analysis population and time point description | Pure ITT Population Day 28 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1038 | 510 |
| | COR-ITT-D28 (N (%)) | 938 (90.37%) | 459 (90.00%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -2.80% |
| | | P-value | 0.820 |
| Analysis population and time point description | Pure ITT Population Day 42 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1038 | 510 |
| | COR-ITT-D42 (N (%)) | 895 (86.22%) | 442 (86.67%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -4.06% |
| | | P-value | 0.811 |
| Notes | CI LL = Confidence Interval Lower Limit | | |
| Analysis description | Secondary analysis S2: UNC-MITT-D14, UNC-MITT-D28, UNC-MITT-D42 UNC-PP-D14, UNC-PP-D28, UNC-PP-D42 UNC-ITT-D14, UNC-ITT-D28, UNC -ITT-D42 | | |
| Analysis population and time point description | Modified-ITT Population Day 14 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | UNC-MITT-D14 (N (%)) | 969 (94.35%) | 474 (95.37%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -3.34% |
| | | P-value | 0.405 |
| Analysis population and time point description | Modified-ITT Population Day 28 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |

| | | | |
|--|-----------------------------------|-----------------------|---------------|
| | UNC-MITT-D28 (N (%)) | 910 (88.61%) | 391 (78.67%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | 5.84% |
| | | P-value | <0.001 |
| Analysis population and time point description | Modified-ITT Population Day 42 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | UNC-MITT-D42 (N (%)) | 769 (74.88%) | 330 (66.40%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | 3.55% |
| | | P-value | <0.001 |
| Analysis population and time point description | Per Protocol Population Day 14 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | UNC-PP-D14 (N (%)) | 924 (97.16%) | 448 (96.97%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -1.69% |
| | | P-value | 0.841 |
| Analysis population and time point description | Per Protocol Population Day 28 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | UNC-PP-D28 (N (%)) | 884 (92.95%) | 376 (81.39%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | 7.67% |
| | | P-value | <0.001 |
| Analysis population and time point description | Per Protocol Population Day 42 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | UNC-PP-D42 (N (%)) | 746 (78.44%) | 319 (69.05%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | 4.44% |
| | | P-value | <0.001 |
| Analysis population and time point description | Pure ITT Population Day 14 | | |

| | | | |
|--|---|-----------------------|--------------------|
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1038 | 510 |
| | UNC-ITT-D14 (N (%)) | 975 (93.93%) | 481 (94.31%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | -2.86% |
| | | P-value | 0.764 |
| Analysis population and time point description | Pure ITT Population Day 28 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1038 | 510 |
| | UNC-ITT-D28 (N (%)) | 910 (87.67%) | 391 (76.67%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | 6.82% |
| | | P-value | <0.001 |
| Analysis population and time point description | Pure ITT Population Day 42 | | |
| Descriptive statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1038 | 510 |
| | UNC-ITT-D42 (N (%)) | 769 (74.08%) | 330 (64.71%) |
| Effect estimate per comparison | | Comparison groups | DHA/PQP – A/L |
| | | 97.5% one-sided CI LL | 4.45% |
| | | P-value | <0.001 |
| Notes | CI LL = Confidence Interval Lower Limit | | |
| Analysis description | Secondary analysis S3: Early, Late and True Treatment Failures (ETF, LTF and True) | | |
| Analysis population and time point description | Pure ITT Population Day 28 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1038 | 510 |
| | ETF (N (%)) | 12 (1.16%) | 2 (0.39%) |
| | LTF (N (%)) | 62 (5.97%) | 85 (16.67%) |
| | ETF+LTF (N (%)) | 74 (7.13%) | 87 (17.06%) |
| | True (N (%)) | 38 (3.66%) | 14 (2.75%) |
| Effect estimate per comparison | ETF+LTF | Comparison groups | DHA/PQP – A/L |
| | | 95% CI | (-13.55% ; -6.31%) |
| | | P-value | <0.001 |
| | True | Comparison groups | DHA/PQP – A/L |
| | | 95% CI | (-0.91% ; 2.74%) |
| | | P-value | 0.347 |
| Analysis population and time point description | Modified-ITT Population Day 28 | | |

| | | | |
|--|--|-------------------|--------------------|
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | ETF (N (%)) | 12 (1.17%) | 2 (0.40%) |
| | LTF (N (%)) | 62 (6.04%) | 85 (17.10%) |
| | ETF+LTF (N (%)) | 74 (7.21%) | 87 (17.51%) |
| | True (N (%)) | 38 (3.70%) | 14 (2.82%) |
| Effect estimate per comparison | ETF+LTF | Comparison groups | DHA/PQP – A/L |
| | | 95% CI | (-14.00% ; -6.60%) |
| | | P-value | <0.001 |
| | True | Comparison groups | DHA/PQP – A/L |
| | | 95% CI | (-0.97% ; 2.74%) |
| | | P-value | 0.373 |
| Analysis population and time point description | Per Protocol Population Day 28 | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | ETF (N (%)) | 1 (0.11%) | 0 |
| | LTF (N (%)) | 51 (5.36%) | 74 (16.02%) |
| | ETF+LTF (N (%)) | 52 (5.47%) | 74 (16.02%) |
| | True (N (%)) | 26 (2.73%) | 12 (2.60%) |
| Effect estimate per comparison | ETF+LTF | Comparison groups | DHA/PQP – A/L |
| | | 95% CI | (-14.19% ; -6.91%) |
| | | P-value | <0.001 |
| | True | Comparison groups | DHA/PQP – A/L |
| | | 95% CI | (-1.65% ; 1.92%) |
| | | P-value | 0.882 |
| Analysis description | Secondary analysis S4: Aparasitaemic patients and time to parasitaemia clearance | | |
| Analysis population and time point description | Modified-ITT Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | Aparasitaemic at Day 0 (N (%)) | 1 (0.10%) | 1 (0.20%) |
| | Aparasitaemic at Day 1 (N (%)) | 370 (36.03%) | 142 (28.57%) |
| | Aparasitaemic at Day 2 (N (%)) | 863 (84.03%) | 420 (84.51%) |
| | Aparasitaemic at Day 3 (N (%)) | 1003 (97.66%) | 489 (98.39%) |
| Kaplan-Meier estimate | Median time to parasitaemia clearance (days) | 2 | 2 |
| Analysis population and time point description | Per Protocol Population | | |

| | | | |
|--|--|-------------------|-------------------|
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | Aparasitaemic at Day 0 (N (%)) | 0 | 0 |
| | Aparasitaemic at Day 1 (N (%)) | 351 (36.91%) | 133 (28.79%) |
| | Aparasitaemic at Day 2 (N (%)) | 815 (85.70%) | 392 (84.85%) |
| | Aparasitaemic at Day 3 (N (%)) | 939 (98.74%) | 457 (98.92%) |
| Kaplan-Meier estimate | Median time to parasitaemia clearance (days) | 2 | 2 |
| Analysis description | Secondary analysis S5: Afebrile patients and time to fever clearance | | |
| Analysis population and time point description | Modified-ITT Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | Afebrile at Day 0 (N (%)) | 413 (40.21%) | 200 (40.24%) |
| | Afebrile at Day 1 (N (%)) | 919 (89.48%) | 421 (84.71%) |
| | Afebrile at Day 2 (N (%)) | 1001 (97.47%) | 483 (97.18%) |
| | Afebrile at Day 3 (N (%)) | 1000 (97.37%) | 491 (98.79%) |
| Kaplan-Meier estimate | Median time to fever clearance (days) | Not available (*) | Not available (*) |
| Notes | (*) It could not be calculated because of too few assessment timepoints | | |
| Analysis population and time point description | Per Protocol Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | Afebrile at Day 0 (N (%)) | 388 (40.80%) | 185 (40.04%) |
| | Afebrile at Day 1 (N (%)) | 855 (89.91%) | 394 (85.28%) |
| | Afebrile at Day 2 (N (%)) | 935 (98.32%) | 451 (97.62%) |
| | Afebrile at Day 3 (N (%)) | 934 (98.21%) | 459 (99.35%) |
| Kaplan-Meier estimate | Median time to fever clearance (days) | Not available (*) | Not available (*) |

| | | | |
|---|---|----------------|----------------|
| Notes | (*) It could not be calculated because of too few assessment timepoints | | |
| Analysis description | Secondary analysis S6: Patients with gametocytes at various timepoints | | |
| Analysis population and time point description | Modified-ITT Population | | |
| Descriptive Statistics Number of patients with gametocytes (N (%)) | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | Day 0 | 121 (11.78%) | 66 (13.28%) |
| | Day 7 | 91 (8.86%) | 21 (4.23%) |
| | Day 14 | 47 (4.58%) | 1 (0.20%) |
| | Day 28 | 6 (0.58%) | 3 (0.60%) |
| | Day 42 | 11 (1.07%) | 7 (1.41%) |
| Analysis population and time point description | Per Protocol Population | | |
| Descriptive Statistics Number of patients with gametocytes (N (%)) | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | Day 0 | 108 (11.36%) | 60 (12.99%) |
| | Day 7 | 86 (9.04%) | 19 (4.11%) |
| | Day 14 | 43 (4.52%) | 1 (0.22%) |
| | Day 28 | 4 (0.42%) | 2 (0.43%) |
| | Day 42 | 10 (1.05%) | 7 (1.52%) |
| Analysis description | Secondary analysis S7: Haematological Recovery | | |
| Analysis population and time point description | Safety/Pure ITT Population | | |
| Descriptive Statistics Hb (g/L) mean (std) | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1038 | 510 |
| | Day 0 | 89.23 (18.15) | 90.59 (18.20) |
| | Nadir (Day 3) | 85.86 (16.68) | 85.72 (17.43) |
| | Day 28 | 104.90 (14.26) | 104.79 (16.77) |
| Analysis description | Secondary analysis S8: Compliance with study treatment: Patients having taken at least 80% of the scheduled study treatment | | |
| Analysis population and time point description | Safety/Pure ITT Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1038 | 510 |
| | Compliance ≥80% | 1027 (98.94%) | 507 (99.41%) |
| Analysis population and time point description | Modified-ITT Population | | |
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 1027 | 497 |
| | Compliance ≥80% | 1016 (98.93%) | 494 (99.40%) |
| Analysis population and time point description | Per Protocol Population | | |

| | | | |
|------------------------|------------------------|------------|------------|
| Descriptive Statistics | Treatment group | DHA/PQP | A/L |
| | Number of subjects | 951 | 462 |
| | Compliance $\geq 80\%$ | 951 (100%) | 462 (100%) |

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant has not integrated or compared the efficacy data between the two Phase III studies due to the many differences in population and the potential effects of geographical region and parasites on the outcomes. This omission is considered to be appropriate.

Clinical studies in special populations

Not applicable

Supportive studies

The two phase I/II studies were single centre, single arm studies and were aimed at investigating the PK profile of DHA/PQP and were definitively underpowered to draw any conclusion on cure rates. Therefore, the analyses of all efficacy endpoints were carried out only at a descriptive level. Efficacy was not the primary objective of these studies, but was examined as secondary objective.

A total of 32 patients were recruited into the African study (DM 04008) and 25 patients were recruited in the Asian study (DM 04009). In general, the medical history for the patients in both Phase I/II studies is consistent with acute malaria.

The same three day, weight-based dose regimen and timing of the dose was used in the Phase I/II studies as for the Phase III studies. The dosing regimen in the African Phase I/II study provided for a potential dose of between 1.6-3.6 mg/kg/day DHA and 12.8-29.1 mg/kg/day PQP. In the Asian Phase I/II study, the regimen provided for a potential daily dose of 1.6-3.6 mg/kg/day DHA and 12.8-29.1 mg/kg/day PQP.

All secondary endpoints recorded in Phase III studies (with the exception of gametocytes) were recorded also in the Phase I/II studies.

Results

- In the African study there was one ETF. The number of LTF was equal to three at Day 28, 14 at Day 42 and 25 at Day 90.
- There was no ETF and only one LTF (at Day 56) in the Asian study.
- The true treatment failures as defined by WHO were not estimated in the Phase I/II studies.
- In the Asian study, all patients were clear of parasitaemia by Day 7, while in the African study all patients were clear of parasitaemia by Day 2.
- In the Asian study, all the patients were afebrile by Day 2, while in the African study all the patients were afebrile by Day 1.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme included two well conducted Phase III clinical trials. These were designed to reflect the differences in baseline immunity and transmission risks for malaria in the differing endemic regions. Thus, studies were considered separately due to the many differences in populations and the potential effects of geographical region and parasites on the outcomes. Both trials had an acceptable open label design.

Efficacy data and additional analyses

Both trials met the primary endpoint demonstrating non-inferiority of DHA/PQP to the appropriate comparator for treatment of patients with uncomplicated *P. falciparum* malaria. The true treatment failure rates in the two pivotal studies were 1.8% and 2.8% for studies DM 040010 and DM 040011 respectively. These are well within the current standard of 5% set by the WHO. Eurartesim was non-inferior to comparators regarding the rates of recrudescence and new infection. Indeed, for both trials, Eurartesim was statistically and clinically superior to the comparator combinations for uncorrected cure rate and the rate of new infections at all time points starting from Day 28. Data indicated however that for both studies, DHA/PQP has a lesser gametocytocidal effect than comparator.

2.5.4. Conclusions on the clinical efficacy

Eurartesim has been shown to be non-inferior to established standard-of-care comparator drugs in each of two large, well-designed pivotal studies performed in two different malaria-endemic regions. For both studies, the results have been shown to be robust based on several sensitivity analyses.

2.6. Clinical safety

Due to major differences between the studies, safety data have been addressed separately by study under each sub-headings below. With very small numbers in the two preliminary studies in adults and children, most attention was given to the data from the Phase III studies DM 040010 and DM 040011

Patient exposure

The safety database for exposure to DHA/PQP consists primarily of data from the five clinical studies sponsored by Sigma-tau. The total database includes 1862 adult and paediatric patients with malaria.

The two pivotal Phase III clinical trials were designed to reflect the differences in baseline immunity and transmission risks for malaria in the differing endemic regions. For these studies, the three study populations investigated were: the pure-Intention to Treat (ITT), the modified ITT (m-ITT) and the per protocol (PP) population. The ITT population was the same population as the safety population, which was defined as all randomised patients who received at least one dose of the study treatment. This definition was also used in the Phase I/II and in the healthy volunteer study.

The demographic and baseline characteristics of the populations in Phase III trials are displayed in the following table:

Table 53: Overall Demographic and Baseline Characteristics – Phase III Studies (Safety Population)

| Demographic and Baseline Characteristics | ST3073+ST3074 DM40010 | | ST3073+ST3074 DM40011 | |
|--|-----------------------|---------------|-----------------------|--------------|
| | DHA/PQP | AS+MQ | DHA/PQP | A/L |
| N | 767 | 381 | 1038 | 510 |
| Gender: | | | | |
| Male | 582 (75.88%) | 295 (77.43%) | 525 (50.58%) | 281 (55.10%) |
| Female | 185 (24.12%) | 86 (22.57%) | 513 (49.4%) | 229 (44.9%) |
| Mean Age (SD) (Years) | 25.44 (±13.25) | 25.79(±13.68) | 2.42 (±1.14) | 2.43(±1.16) |
| Race: | | | | |
| Asian | 767 (100%) | 381 (100%) | 1 (0.10%) | 0 |
| Black | | | 1036 (99.81%) | 510 (100%) |
| Other Race | | | 1 (0.10%) | 0 |
| Mean Weight (±SD) (kg) | 44.34(±15.10) | 44.61(±15.13) | 11.19(±2.55) | 11.28(±2.67) |
| Parasite Density at Baseline: | | | | |
| Median | 10,174 | 9,792 | 27,222.5 | 28,711.0 |
| Range | 80-204,276 | 80-196,438 | 0 - 325,866 | 0 - 398,545 |
| Fever at Baseline: | 37.89 (±1.01) | 37.93(±1.02) | 37.88 (±1.22) | 37.86(±1.18) |
| Haemoglobin at Baseline (g/L) | | | | |
| <70 | 28 (3.65%) | 7 (1.84%) | 141 (13.58%) | 63 (12.35%) |
| ≥70 | 735 (95.83%) | 372 (97.64%) | 871 (83.91%) | 433 (84.90%) |

- **DM 040010:** In the m-ITT population the proportions vomiting within 30 min of dosing were 1.1% for both treatments but the proportion of patients vomiting 30-60 min after dosing was higher in the DHA/PQP group (1.5% vs. 0.3%). Vomiting was reported as a presenting complaint in 28% in each treatment group so may have partly reflected acute malaria. Vomiting was reported as a treatment emerging adverse event (TEAE) at any time during the study in 2.5% DHA/PQP and 6.3% AS+MQ patients groups while persistent vomiting leading to withdrawal before Day 63 occurred in four DHA/PQP patients.
- **DM 040011:** The highest incidence of vomiting occurred within 30 min of taking the first dose on Day 0 (10.6% and 9.6% per group). Over the three dosing days, 17.3% and 14.1% in respective treatment groups vomited at least once. Vomiting was reported as a presenting complaint in 13.9% and 12.2% and was reported as a TEAE at any time during the study in 6.8% in each group. Persistent vomiting led to study withdrawal before Day 28 in 22 children in the DHA/PQP group and 4 in the A/L group.

Adverse events

DM 040010: The proportions experiencing at least one TEAE were comparable between treatments (69% DHA/PQP and 72% AS+MQ). The greater number of malaria AEs in the AS+MQ group was consistent with more new *P. falciparum* and non-*falciparum* infections in this group.

The table shows some AEs for which differences in rates between treatment groups were $\geq 2\%$.

Table 54: TEAEs with Differences ($>\pm 2\%$) Between Treatment Groups (Safety Population)

| System Organ Class | DHA/PQP | | AS+MQ | |
|---|---------|-------|-------|-------|
| | n | % | n | % |
| Cardiac Disorders | 68 | 8.87 | 15 | 3.94 |
| Sinus Bradycardia | 32 | 4.17 | 5 | 1.31 |
| Gastrointestinal Disorders | 88 | 11.47 | 66 | 17.32 |
| Nausea | 22 | 2.87 | 26 | 6.82 |
| Vomiting | 19 | 2.48 | 24 | 6.30 |
| General Disorders & Administration Site Conditions | 103 | 13.43 | 60 | 15.75 |
| Asthenia | 38 | 4.95 | 29 | 7.61 |
| Infections and Infestations | 313 | 40.81 | 161 | 42.26 |
| Malaria | 111 | 14.47 | 86 | 22.57 |
| Nervous System Disorders | 150 | 19.56 | 100 | 26.25 |
| Dizziness | 11 | 1.43 | 24 | 6.30 |
| Headache | 138 | 17.99 | 77 | 20.21 |
| Psychiatric Disorders | 5 | 0.65 | 13 | 3.41 |

The table below shows some of the differences between treatments for certain types of drug-related AEs. The rates of cardiac AEs considered related were 3.5% for DHA/PQP and 2.1% for AS+MQ.

Table 55: Related TEAEs with Differences ($>\pm 2\%$) Between Treatment Groups (Safety Population)

| System Organ Class | DHA/PQP | | AS+MQ | |
|---|---------|------|-------|------|
| | n | % | n | % |
| Gastrointestinal Disorders | 12 | 1.56 | 21 | 5.51 |
| Nausea | 2 | 0.26 | 12 | 3.15 |
| General Disorders and Administration Site Conditions | 21 | 2.74 | 16 | 4.20 |
| Asthenia | 12 | 1.56 | 14 | 3.67 |
| Nervous System Disorders | 36 | 4.69 | 26 | 6.82 |
| Dizziness | 4 | 0.52 | 13 | 3.41 |

The higher rate of cardiac AEs (all and related) in the DHA/PQP group was explored further. The individual preferred terms (PTs) are shown below by relationship and severity.

Table 56: TEAEs Summarised by Maximum Severity and Relationship to Study Treatment Only Cardiac AEs Safety Population

| System Organ Class & Preferred Term | DHA/PQP (N=767) | | | | | | AS+MQ (N=381) | | | | | |
|-------------------------------------|-----------------|-------------------|-----------------|---------------|-------------------|-----------------|---------------|-------------------|-----------------|---------------|-------------------|-----------------|
| | Related | | | Not Related | | | Related | | | Not Related | | |
| | Mild n (%) | Moderate n (%) | Severe n (%) | Mild n (%) | Moderate n (%) | Severe n (%) | Mild n (%) | Moderate n (%) | Severe n (%) | Mild n (%) | Moderate n (%) | Severe n (%) |
| Cardiac disorders | | | | | | | | | | | | |
| At Least One | 27 (3.52%) | 0 | 0 | 42 (5.48%) | 0 | 0 | 8 (2.10%) | 0 | 0 | 7 (1.84%) | 0 | 0 |
| Atrioventricular Block First Degree | 0 | 0 | 0 | 4 (0.52%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bundle Branch Block | 1 (0.13%) | 0 | 0 | 5 (0.65%) | 0 | 0 | 0 | 0 | 0 | 1 (0.26%) | 0 | 0 |
| Bundle Branch Block Left | 0 | 0 | 0 | 1 (0.13%) | 0 | 0 | 1 (0.26%) | 0 | 0 | 0 | 0 | 0 |
| Bundle Branch Block Right | 0 | 0 | 0 | 5 (0.65%) | 0 | 0 | 2 (0.52%) | 0 | 0 | 1 (0.26%) | 0 | 0 |
| Extrasystoles | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.26%) | 0 | 0 | 0 | 0 | 0 |
| Myocardial Infarction | 1 (0.13%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Palpitations | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.26%) | 0 | 0 |
| Sinus Arrhythmia | 7 (0.91%) | 0 | 0 | 2 (0.26%) | 0 | 0 | 1 (0.26%) | 0 | 0 | 3 (0.79%) | 0 | 0 |
| Sinus Bradycardia | 7 (0.91%) | 0 | 0 | 25 (3.26%) | 0 | 0 | 1 (0.26%) | 0 | 0 | 4 (1.05%) | 0 | 0 |
| Sinus Tachycardia | 13 (1.69%) | 0 | 0 | 1 (0.13%) | 0 | 0 | 2 (0.52%) | 0 | 0 | 0 | 0 | 0 |
| Tachycardia | 1 (0.13%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ventricular Dysfunction | 0 | 0 | 0 | 1 (0.13%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ventricular Extrasystoles | 1 (0.13%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ventricular Hypertrophy | 0 | 0 | 0 | 3 (0.39%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Wolff-Parkinson-White Syndrome | 1 (0.13%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

The applicant stated that most cases of sinus bradycardia or tachycardia consisted of heart rates that were borderline when measured by the core ECG laboratory and were deemed to be of minor clinical significance. Also, some reports did not correspond to the heart rate measured by the physician during the visit or that measured by the ECG core laboratory. In the DHA/PQP group there was a slightly greater frequency of bradycardia, sinus tachycardia and arrhythmias as compared to the AS+MQ group.

Sinus bradycardia, sinus tachycardia and sinus arrhythmia accounted for most of the overall difference in "cardiac TEAEs" between the DHA/PQP and AS+MQ groups. All these TEAEs were considered by the investigators to be of mild intensity but the basis for the investigators' grading of these events is not clear. In addition, rates for bradycardia and tachycardia were clearly higher in the DHA/PQP group. Review of cases of sinus bradycardia and tachycardia showed that most were present on ECG but were not identified by the physician at the corresponding study visit. In many cases the rates were just outside of the normal limits and the subjects were asymptomatic. However, heart rates > 120 bpm seem to have occurred in 35 subjects and rates > 130 bpm in 7 subjects.

The overall proportions with mild, moderate and severe TEAEs were comparable between treatment groups (55.2%, 12.4% and 1.8% for DHA/PQP and 57.7%, 12.6% and 2.1% for AS+MQ). The most frequently reported AEs (related and unrelated) in the DHA/PQP and AS+MQ groups were headache (18% vs. 20%), malaria (14.5% vs. 22.6%), *P. falciparum* malaria (13.4% vs. 15.2%) and pyrexia (10.6% vs. 11.3%).

Subjective fever was reported by 58.3% (mild), 18.4% (moderate) and 0.3% (severe) in the DHA/PQP group and by 56.7% (mild), 20% (moderate) and 0.8% (severe) in the AS+MQ group. Headache was reported by 41% (mild) and 18% (moderate) in the DHA/PQP group and by 37.8% (mild), 21% (moderate) and 0.3% (severe) in the AS+MQ group. Nausea was reported less often in the DHA/PQP group with rates of 11.3% mild and 0.4% moderate vs. 17.3% mild and 1.3% moderate. Similarly, vomiting was reported with rates of 6.1% mild and 0.4% moderate (DHA/PQP) vs. 9.7% mild and 0.8% moderate (AS+MQ).

Adverse event of special interest

In this study baseline and pre-dose Day 2 12-lead ECGs were obtained. These were viewed during recording and transmitted directly to MDS Central Telemedicine Department in France for interpretation and reporting except for ECGs from centre 19 (Thailand) where paper ECGs were printed and then sent to MDS Pharma. The ECGs were measured semi-automatically on a superimposed representative complex.

The descriptive analysis of mean values showed a highly statistically significant difference between treatments in the change in QTcB and QTcF intervals from baseline to Day 2 (ANOVA, $p < 0.001$) with longer intervals in the DHA/PQP group. The Day 2 change in QTc from baseline was statistically significantly different between treatments by both Bazett's and Fridericia's methods. At Day 7 the difference in QTcF was significant but slightly fewer patients in the DHA/PQP group (1.8%) showed an increase in QTc > 60 ms compared with the AS+MQ group (2.9%).

Table 57: Descriptive ECG Analyses (Mean) During the Study – DHA/PQP (Safety Population)

| Day | n | HR | PR | QT | QTcB | QTcF |
|----------------------|-----|-------|--------|--------|--------|--------|
| 0 | 765 | 94.37 | 142.89 | 338.67 | 415.80 | 387.70 |
| 2 | 758 | 72.35 | 149.66 | 393.22 | 421.10 | 410.87 |
| Δ Days 0 to 2 | 752 | - | - | 54.18 | 5.17 | 22.93 |
| 7 | 728 | 80.50 | 148.14 | 366.45 | 416.13 | 398.29 |
| Δ Days 0 to 7 | 726 | - | - | 27.62 | 0.26 | 10.47 |

Table 58: Descriptive ECG Analyses (Mean) During the Study – AS+MQ (Safety Population)

| Day | n | HR | PR | QT | QTcB | QTcF |
|----------------------|-----|-------|--------|--------|--------|--------|
| 0 | 377 | 94.20 | 142.34 | 337.14 | 413.29 | 385.54 |
| 2 | 376 | 74.67 | 150.04 | 378.69 | 412.62 | 400.35 |
| Δ Days 0 to 2 | 370 | - | - | 41.39 | -0.83 | 14.65 |
| 7 | 358 | 78.92 | 147.62 | 369.88 | 415.31 | 399.06 |
| Δ Days 0 to 7 | 353 | - | - | 33.03 | 1.60 | 13.39 |

There was no statistically significant difference between treatments in the proportion of patients with QTc > 500 ms by either method at any time during the study. Three patients experienced prolonged (i.e. > 500 ms) QTcF intervals and four patients experienced prolonged QTcB intervals. These patients (five in total) were all recruited to the DHA/PQP group.

Table 59: QTc (QTcB & QTcF) Values Classified as >500 msec or ≤500 msec. (Safety Population)

| Day | DHA/PQP (n = 767) | | | | | | AS+MQ (n = 381) | | | | | |
|-------------|-------------------|-----|----------|-----|----------|------|-----------------|-----|----------|-----|----------|------|
| | Missing | | QTc >500 | | QTc ≤500 | | Missing | | QTc >500 | | QTc ≤500 | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| QTcB | | | | | | | | | | | | |
| 0 | 3 | 0.4 | 1 | 0.1 | 763 | 99.5 | 4 | 1.1 | 2 | 0.5 | 375 | 98.4 |
| 2 | 13 | 1.7 | 4 | 0.5 | 750 | 97.8 | 8 | 2.1 | 0 | - | 373 | 97.9 |
| 7 | 39 | 5.1 | 0 | - | 728 | 94.9 | 25 | 6.6 | 0 | - | 356 | 93.4 |
| QTcF | | | | | | | | | | | | |
| 0 | 3 | 0.4 | 0 | - | 764 | 99.6 | 4 | 1.1 | 1 | 0.3 | 376 | 98.7 |
| 2 | 13 | 1.7 | 3 | 0.4 | 751 | 97.9 | 8 | 2.1 | 0 | - | 372 | 97.9 |
| 7 | 39 | 5.1 | 0 | - | 728 | 94.9 | 25 | 6.6 | 0 | - | 356 | 93.4 |

The comparison of QTcB means on D0 and D2 shows that in both treatment groups the values were greater for female subjects but the mean change from baseline in the DHA/PQP group was smaller for female subjects (3.14 ms vs. 5.80 ms in male subjects) while corresponding values by gender in the AS+MQ group were 4.73 ms and -2.44 ms. The overall comparison between treatments for changes from baseline and the comparison for male subjects only were statistically significant ($p < 0.001$) with larger changes in the DHA/PQP group. In contrast the comparison for female subjects only did not reach significance ($p = 0.610$). The actual changes in QTcF values were greater than those observed when using the QTcB data. Actual mean values on D0 and D2 were not consistently or notably greater in female vs. male subjects. However, the same pattern of findings as for QTcB applied to the analysis of changes from baseline overall and by gender.

Table 60: QTcF by Gender and Overall – Asian study (Safety Population)

| Treatment | Visit | Gender | N | Nmiss | Mean | STD | 95% CI |
|-----------|--------|---------|-----|-------|--------|-------|-----------------------------|
| DHA/PQP | Day 0 | Females | 185 | 0 | 390.87 | 29.01 | 386.66, 395.08 |
| | | Males | 579 | 3 | 386.69 | 24.17 | 384.72, 388.66 |
| | | Overall | 764 | 3 | 387.70 | 25.47 | 385.89, 389.51 |
| | Day 2 | Females | 179 | 6 | 410.06 | 27.66 | 405.98, 414.14 |
| | | Males | 575 | 7 | 411.12 | 24.78 | 409.09, 413.15 |
| | | Overall | 754 | 13 | 410.87 | 25.48 | 409.04, 412.69 |
| | Change | Females | 179 | 6 | 18.60 | 24.25 | 15.03, 22.18 ⁽¹⁾ |
| | | Males | 573 | 9 | 24.28 | 22.76 | 22.41, 26.15 ⁽²⁾ |
| | | Overall | 752 | 15 | 22.93 | 23.23 | 21.26, 24.59 ⁽³⁾ |
| AS+MQ | Day 0 | Females | 85 | 1 | 383.64 | 26.89 | 377.84, 389.43 |

| | | | | | | | |
|--|---|---------|-----|----|--------|-------|-----------------------------|
| | | Males | 292 | 3 | 386.09 | 25.22 | 383.19, 389.00 |
| | | Overall | 377 | 4 | 385.54 | 25.59 | 382.95, 388.13 |
| | Day 2 | Females | 83 | 3 | 404.02 | 23.18 | 398.96, 409.09 |
| | | Males | 290 | 5 | 399.30 | 20.70 | 396.91, 401.70 |
| | | Overall | 373 | 8 | 400.35 | 21.34 | 398.18, 402.53 |
| | Change | Females | 83 | 3 | 19.12 | 22.90 | 14.12, 24.12 ⁽¹⁾ |
| | | Males | 287 | 8 | 13.35 | 23.96 | 10.57, 16.14 ⁽²⁾ |
| | | Overall | 370 | 11 | 14.65 | 23.81 | 12.21, 17.08 ⁽³⁾ |
| | ⁽¹⁾ test for the comparison DHA/PQP vs. AS+MQ for females: p-value = 0.868 ⁽²⁾ test for the comparison DHA/PQP vs. AS+MQ for males: p-value < 0.001 ⁽³⁾ test for the comparison DHA/PQP vs. AS+MQ overall: p-value < 0.001 | | | | | | |

Subjects aged < 16 years in both treatment groups showed greater mean QTcB values vs. older subjects on D0 and D2 and greater changes from baseline. The comparison between treatments for changes from baseline was statistically significant ($p < 0.001$) overall and for those aged ≥ 16 years with greater changes in the DHA/PQP group but there was only a numerical difference for the younger subjects. In contrast, the QTcF data on D0 and D2 showed that actual values were smaller in those aged < 16 years. Nevertheless, as for QTcB, the comparison between treatments for changes from baseline was significant ($p < 0.001$) overall and for those aged ≥ 16 years with greater changes in the DHA/PQP group but there was only a numerical difference for the younger subjects. The magnitude of the difference in change between treatment groups was 4.76 ms for those aged < 16 years and 9.25 ms for the older age group.

The applicant observes that there was no gender imbalance for total TEAEs in the two SOC. In the DHA/PQP group subjects aged < 16 years had a higher rate of cardio-vascular TEAEs (21.4% vs. 11.8%), which reflects the rates of sinus tachycardia (6.9% vs. 2.4%) and QTc prolongation (12.7% vs. 5.7%).

DM 040011

The proportion of patients experiencing at least one TEAE was similar between treatment groups (79.3% DHA/PQP and 80.6% A/L). The table shows some AEs for which differences in rates between treatment groups were $\geq 2\%$.

Table 61: TEAEs with Differences ($\geq 2\%$) Between Treatment Groups (Safety Population)

| <i>System Organ Class</i> | Proportion of Patients (%) | |
|---|-----------------------------------|------------|
| TEAE | DHA/PQP | A/L |
| <i>Blood and Lymphatic</i> | 7.32 | 10.20 |
| <i>General Disorders and Administration Site Conditions</i> | 30.25 | 32.94 |
| Pyrexia | 29.09 | 31.96 |
| <i>Infections and Infestations</i> | 46.63 | 52.94 |
| Influenza | 21.00 | 18.63 |
| <i>P. falciparum</i> infection | 18.98 | 25.88 |

The proportions of patients with mild, moderate and severe TEAEs were comparable between treatment groups at 50.3%, 25.6% and 3.4% respectively for DHA/PQP compared with 49.2%, 28.4% and 2.9% respectively for A/L. The overall proportions of patients with treatment-related TEAEs were also comparable between treatments (71% DHA/PQP and 72% A/L). The table shows some differences for drug-related AEs that occurred at rates $\geq 2\%$.

Table 62: Related TEAEs with Differences ($\geq 2\%$) Between Treatment Groups (Safety Population)

| <i>System Organ Class</i> | Proportion of Patients (%) | |
|---|-----------------------------------|------------|
| TEAE | DHA/PQP | A/L |
| <i>Blood and Lymphatic</i> | 7.13 | 9.22 |
| <i>General Disorders and Administration Site Conditions</i> | 23.60 | 25.69 |
| <i>Infections and Infestations</i> | 36.51 | 41.57 |
| Influenza | 15.99 | 13.92 |
| <i>P. falciparum</i> infection | 14.07 | 19.41 |
| <i>Metabolism and Nutrition</i> | 5.49 | 7.25 |
| Anorexia | 5.20 | 7.25 |

In both treatment groups cough was the most frequently reported AE with rates of 39.8% and 32% related for DHA/PQP compared to 38% and 31% related for A/L. However, it is not understood why cough might have been considered drug-related by investigators. Cough was considered most often associated with influenza, pneumonia and *P. falciparum* infection. Pyrexia was reported with rates of 29.1% and 22.4% related in the DHA/PQP group compared to 32% and 24.3% related in the A/L group. Pyrexia was often temporally associated with cough, influenza, *P. falciparum* infection, diarrhoea and vomiting. There were no arrhythmias reported during the study.

Using Bazett's method the proportions of patients with normal, borderline or prolonged QTc intervals at baseline were 80.4%, 14.6% and 3.7% for DHA/PQP compared to 79.8%, 13.9% and 5.5% for A/L.

However, on Day 2 the pre-dose ECGs showed that a statistically significantly higher proportion of patients in the DHA/PQP group (60.3%, 29.1% and 9.1% with normal, borderline and prolonged QTc intervals) had borderline QTc intervals compared to the A/L group (72.2%, 19.8% and 6.9% respectively) and the proportion with prolonged QTc was numerically higher.

There was no significant difference between treatment groups in the proportion of patients with QTc intervals >500 ms (e.g. two per group on Day 2). Change in QTc interval from baseline to Day 2 showed less QTc shortening and more prolongation in the DHA/PQP group compared with A/L (Mantel-Haenszel Chi-square test, $p < 0.001$). In the DHA/PQP group, 46.7% had an increase <30 ms, 19.6% had a prolongation 30 - 60 ms and 2.7% had a prolongation >60 ms. These rates compare with 46.1%, 13.5% and 2%, respectively, in the A/L group.

Using Fridericia's method the proportions of patients with normal, borderline and prolonged QTc intervals were not significantly different between treatments at any visit and the only QTc value >500 ms occurred in one patient on Day 2 in the A/L group. However, as for QTcB, the increase in QTc intervals from baseline was statistically significantly greater for DHA/PQP on Day 2.

Descriptive analyses showed a highly statistically significant difference between treatments in the change in QT, QTc Bazett and QTc Fridericia values from baseline to Day 2.

Table 63: Descriptive ECG Analyses (Means) During the Study (Safety Population)

| Day | DHA/PQP | | | | | | A/L | | | | | |
|-------------|---------|--------|--------|--------|--------|--------|-----|--------|--------|--------|--------|--------|
| | n | HR | PR | QT | QTcB | QTcF | n | HR | PR | QT | QTcB | QTcF |
| 0 | 1033 | 149.28 | 112.95 | 263.12 | 410.59 | 353.77 | 509 | 149.43 | 112.48 | 263.46 | 411.20 | 354.25 |
| 2 | 1023 | 120.60 | 122.74 | 301.36 | 422.88 | 377.45 | 506 | 124.11 | 121.65 | 293.79 | 418.09 | 371.41 |
| Δ Day 0-2 | | | | 38.25* | 12.20* | 23.64* | | | | 30.54* | 6.95* | 17.30* |
| 7 | 1000 | 125.17 | 122.22 | 286.60 | 409.46 | 363.28 | 496 | 124.44 | 122.49 | 288.37 | 410.58 | 364.67 |
| Δ Day 0-7 | | | | 23.61 | -1.12 | 9.58 | | | | 24.95 | -0.58 | 10.47 |
| 14 | 3 | 122.00 | 124.00 | 285.67 | 406.67 | 361.33 | 1 | 93.00 | 124.00 | 338.00 | 422.00 | 392.00 |
| 28 | 67 | 126.79 | 118.79 | 288.94 | 414.22 | 367.01 | 34 | 136.47 | 118.03 | 280.00 | 415.50 | 363.85 |
| 42 | 19 | 131.00 | 115.83 | 282.94 | 408.33 | 361.11 | 12 | 124.75 | 120.45 | 293.33 | 417.42 | 370.58 |
| Δ Day 0-LAD | 1026 | -24.25 | 9.45 | 24.17 | -0.91 | 9.94 | 506 | -24.77 | 9.89 | 24.43 | -0.72 | 10.28 |

The study report states that the lengthening of QT from baseline to Day 2 was probably due to the fall in HR. Patients were tachycardic throughout the study but particularly so at baseline.

The change in QTcB from baseline to Day 2 is said to be inconclusive and may have been over-corrected whereas the change in QTcF may be clinically significant (i.e. associated with increased risk of arrhythmia) particularly for DHA/PQP.

The QTcB data showed a trend for smaller mean changes from baseline as weight increased in the A/L group. The treatment comparison for changes from baseline was statistically significant ($p < 0.001$) for the weight class from 13 to < 18 kg and overall but not for other classes. The QTcF data did not show a specific trend in either treatment group but the treatment comparison for change from baseline was statistically significant ($p < 0.001$) overall and in the weight classes from 13 to < 18 kg and from 7 to

< 13 kg with greater changes in each case in the DHA/PQP group vs. the A/L group. The comparison for the other weight classes showed numerically greater changes in the DHA/PQP group.

Table 64: QTcF by Weight Class and Overall – African study (Safety Population)

| Treatment | Visit | Weight | N | Nmiss | Mean | STD | 95% CI |
|---|--------|-----------------|------|-------|--------|-------|------------------------------|
| DHA/PQP | Day 0 | < 7 kg | 18 | 1 | 350.83 | 30.97 | 335.43, 366.23 |
| | | >=7 and <13 kg | 734 | 11 | 351.98 | 24.13 | 350.23, 353.73 |
| | | >=13 and <18 kg | 266 | 0 | 358.60 | 22.19 | 355.92, 361.28 |
| | | >=18 kg | 7 | 1 | 365.14 | 22.33 | 344.49, 385.79 |
| | | Overall | 1025 | 13 | 353.77 | 23.93 | 352.30, 355.23 |
| | Day 2 | < 7 kg | 19 | 0 | 374.11 | 27.31 | 360.94, 387.27 |
| | | >=7 and <13 kg | 729 | 16 | 374.16 | 23.36 | 372.46, 375.86 |
| | | >=13 and <18 kg | 266 | 0 | 386.53 | 19.69 | 384.16, 388.91 |
| | | >=18 kg | 8 | 0 | 383.50 | 19.27 | 367.39, 399.61 |
| | | Overall | 1022 | 16 | 377.45 | 23.13 | 376.03, 378.87 |
| | Change | < 7 kg | 18 | 1 | 23.11 | 24.10 | 11.13, 35.09 ⁽¹⁾ |
| | | >=7 and <13 kg | 722 | 23 | 22.13 | 25.99 | 20.24, 24.03 ⁽²⁾ |
| | | >=13 and <18 kg | 266 | 0 | 27.93 | 23.22 | 25.13, 30.74 ⁽³⁾ |
| | | >=18 kg | 7 | 1 | 17.29 | 22.34 | -3.37, 37.94 ⁽⁴⁾ |
| | | Overall | 1013 | 25 | 23.64 | 25.33 | 22.08, 25.20 ⁽⁵⁾ |
| A/L | Day 0 | < 7 kg | 7 | 0 | 356.43 | 45.03 | 314.78, 398.07 |
| | | >=7 and <13 kg | 350 | 4 | 350.74 | 24.02 | 348.21, 353.26 |
| | | >=13 and <18 kg | 142 | 0 | 362.51 | 24.03 | 358.53, 366.50 |
| | | >=18 kg | 7 | 0 | 359.71 | 20.05 | 341.17, 378.26 |
| | | Overall | 506 | 4 | 354.25 | 24.84 | 352.08, 356.41 |
| | Day 2 | < 7 kg | 7 | 0 | 372.00 | 27.98 | 346.12, 397.88 |
| | | >=7 and <13 kg | 348 | 6 | 368.83 | 23.72 | 366.33, 371.33 |
| | | >=13 and <18 kg | 142 | 0 | 377.70 | 18.72 | 374.60, 380.81 |
| | | >=18 kg | 7 | 0 | 371.71 | 22.08 | 351.29, 392.14 |
| | | Overall | 504 | 6 | 371.41 | 22.74 | 369.42, 373.40 |
| | Change | < 7 kg | 7 | 0 | 15.57 | 33.13 | -15.07, 46.21 ⁽¹⁾ |
| | | >=7 and <13 kg | 345 | 9 | 18.31 | 25.81 | 15.58, 21.04 ⁽²⁾ |
| | | >=13 and <18 kg | 142 | 0 | 15.19 | 24.15 | 11.18, 19.20 ⁽³⁾ |
| | | >=18 kg | 7 | 0 | 12.00 | 25.21 | -11.32, 35.32 ⁽⁴⁾ |
| | | Overall | 501 | 9 | 17.30 | 25.42 | 15.07, 19.53 ⁽⁵⁾ |
| ⁽¹⁾ test for the comparison DHA/PQP vs. A+L for patients having weight < 7 kg: p-value = 0.597 | | | | | | | |
| ⁽²⁾ test for the comparison DHA/PQP vs. A+L for patients having weight >=7 and <13 kg: p-value = 0.024 | | | | | | | |
| ⁽³⁾ test for the comparison DHA/PQP vs. A+L for patients having weight >= 13 and <18 kg: p-value < 0.001 | | | | | | | |
| ⁽⁴⁾ test for the comparison DHA/PQP vs. A+L for patients having weight >=18 kg: p-value = 0.685 | | | | | | | |
| ⁽⁵⁾ test for the comparison DHA/POP vs. A+L overall: p-value < 0.001 | | | | | | | |

The actual differences between treatments for the changes in QTcF from baseline were 7.54 ms, 3.82 ms, 12.74 ms and 5.29 ms for ascending weight classes. The applicant points out that only the two middle weight classes included a reasonable sample size and considered the differences to be of a random nature.

Cardiac SOC TEAEs and those coded as ECG abnormalities by weight classes up to 18 kg (there were no such AEs reported in the small numbers with weight > 18 kg) did not suggest any consistent excess of TEAEs in the DHA/PQP group.

Overall view of ECGs

In the applicant's summary and based on patient data (i.e. without taking into account the data from DM09-006) it was concluded that Eurartesim does have a greater potential for QTc prolongation than the comparator drugs against which it was tested but it is stated that the effect is short-lived since it is not apparent at Day 7. It was stated that the cause is uncertain but the regression analysis performed in the patients of the Asian Phase I/II study suggested that QTc prolongation does not correlate with peak plasma concentrations of DHA but with those of PQP. This was later corroborated by the data from DM09-006.

Nevertheless, the D0 and D2 ECGs in subjects with acute malaria were all obtained **pre-dose**. The studies did not capture ECGs around Cmax of either active and therefore the changes from baseline observed in each treatment group are very unlikely to be the maximal changes to be expected during each dose interval.

The QTcF values showed a comparable treatment difference among subjects who were re-dosed due to vomiting in the African study as in all other subjects. Among re-dosed patients there were no statistically significant differences in QTcB values detected for changes from Baseline to Day 2 and Day 7. The QTcF values from Baseline to D2 (but not to D7) showed a statistically significant difference ($p=0.02$) favouring A/L. No subject re-dosed with DHA/PQP had a QTcB or QTcF value over 500 ms on D0, D2 or D7. The maximum change in QTcF was 102 ms on D2 and 78 ms on D7 but the actual maximum QTcF observed was 436 ms on D2 and 430 ms on D7.

The summary also stated that there was no evidence of a corresponding increased risk of AEs associated with QT prolongation. However, the actual numbers are shown below and, while small, there are some imbalances.

Table 65: Incidence of QT-associated TEAEs in Pivotal Studies (Safety Population)

| TEAE | Study DM04010 | | Study DM04011 | | Pooled data | |
|---|-----------------------|--------------------|-------------------------|--------------------|-------------------------|-----------------------|
| | Eurartesim (n=767) | AS + MQ (n=381) | Eurartesim (n=1,038) | Coartem (n=510) | Eurartesim (n=1,805) | Comparator (n=891) |
| Torsade des Pointes | Zero | | Zero | | Zero | |
| Ventricular fibrillation | Zero | | Zero | | Zero | |
| Ventricular flutter | Zero | | Zero | | Zero | |
| Ventricular tachycardia | Zero | | Zero | | Zero | |
| Sudden death | Zero | | 1 (0.1%) | 1 (0.2%) | 1 (0.1%) | 1 (0.1%) |
| Syncope | 1 (0.1%) | 0 (0%) | Zero | | 1 (0.1%) | 0 (0%) |
| Seizure | 0 (0%) | 1 (0.3%) | 4 (0.4%) | 1 (0.2%) | 4 (0.2%) | 2 (0.2%) |
| Seizure (febrile) | Zero | | 2 (0.2%) | 0 (0%) | 2 (0.1%) | 0 (0%) |
| Grand Mal convulsion | 1 (0.1%) | 0 (0%) | Zero | | 1 (0.1%) | 0 (0%) |
| Dizziness | 11 (1.4%) | 24 (6.3%) | Zero | | 11 (0.6%) | 24 (2.7%) |
| QT or QTc prolonged | 43 (5.6%) | 16 (4.2%) | 26 (2.5%) | 13 (2.5%) | 69 (3.8%) | 29 (3.3%) |
| Conduction disorders | 17 (2.2%) | 5 (1.3%) | 1 (0.1%) | 1 (0.2%) | 18 (1.0%) | 6 (0.7%) |
| All cardiac TEAEs | 137 (17.9%) | 45 (11.8%) | 66 (6.4%) | 37 (7.3%) | 203 (11.3%) | 82 (9.2%) |
| Serious cardiac TEAEs | 1 (0.1%) | 0 (0%) | Zero | | 1 (0.1%) | 0 (0%) |
| Discontinuations due to serious cardiac TEAEs | Zero | | Zero | | Zero | |

Serious adverse event/deaths/other significant events

DM 040010

There were no deaths in this study. There were more patients with SAEs in the DHA/PQP group (1.6%) compared with the AS+MQ group (0.8%) but the proportions with SAEs considered drug-related were comparable at 0.8%. In the DHA/PQP group there were twelve SAEs in twelve patients of which six were considered to be related to DHA/PQP (three 'unlikely' and three 'possible'). In the AS+MQ group there were three SAEs in three patients, with relatedness described as one 'unlikely', one 'possible' and one 'probable'.

The six SAEs categorised as related to DHA/PQP included two cases of worsening anaemia considered unlikely to be related, a viral infection requiring hospitalisation on day 51 thought unlikely to be related, a case of Wolff-Parkinson-White (WPW) diagnosed on Day 2 (which the investigator considered possibly related to DHA/PQP even though this is a congenital cardiac conduction anomaly), a grand mal convulsion three hours after the first dose in a 38 year-old male considered possibly related to

DHA/PQP and a case of mild encephalitis on Day 45, which resulted in a left sided hemiplegia thought to be possibly related.

DM 040011

The overall mortality rate was 0.13% (2/1548) with one death in each treatment group. The death in the DHA/PQP group occurred in a 3 year-old whose condition deteriorated suddenly on Day 2. The investigator thought that death was unlikely to be related to DHA/PQP and might have been caused by hypoglycaemia secondary to severe malaria (but there is no glucose result available), hepatitis or septicaemia. The Day 2 ECG was reported as abnormal and heart rate was 163 bpm. A post-mortem examination was not performed.

In the DHA/PQP group 19 SAEs occurred in 18 patients (1.73%) of which 16 were considered related to DHA/PQP but 14 were graded "unlikely". In the A/L group there were five SAEs (1%) of which four were deemed related to study treatment.

The study report states that the overall difference between treatments in SAE rates was mainly due to the higher incidence of infections seen in the DHA/PQP group (n = 13, comprising *P. falciparum* malaria n = 4, pyrexia n = 3, pneumonia = 3, severe malaria n = 1, bronchiolitis n = 1 and gastroenteritis = 1) compared to none in the A/L group.

In the DHA/PQP group two cases of hepatitis were considered possibly and probably related to DHA/PQP:

- One patient aged 2 years developed moderate hepatitis on Day 3 (ALT 236 u/L, mild jaundice (Days 6 - 21) and mild hepatomegaly (Days 7 - 14). On Day 7 hepatitis A serology was positive and hepatitis B and C serology were negative. The hepatitis resolved without intervention by Day 28 and the investigator thought the hepatitis was probably related to DHA/PQP.
- The other patient was aged 4 years and developed severe hepatitis on Day 38. ALT rose from 52 iu/L to 1300.45 iu/L and bilirubin rose from 0.12 mg/dL to 8.08 mg/dL on Days 28 and 42, respectively. Hepatitis B serology was negative and hepatitis A and C serology was not performed. The hepatitis resolved without intervention by Day 59 and the investigator thought this was possibly related to DHA/PQP.

Laboratory findings

DM 040010

Patients were mildly thrombocytopenic at recruitment. Hb, Hct and platelet counts improved and eosinophilia rates increased during the course of the study. All haematological changes were consistent with recovery from malaria and during the course of the study the proportion of patients in both treatment groups with Hct, Hb and platelet counts within the normal range increased.

At enrolment total and direct bilirubin were raised due to haemolysis associated with acute malaria. At the end of the study all biochemical variables were within normal ranges and fewer than 3% of patients showed signs of haemolysis, possibly associated with new infections.

DM 040011

There were overall improvements in anaemia during the study. Non-clinically significant eosinophilia developed in 3.5% per group and shifts in eosinophil counts of approximately 17% (DHA/PQP) and 14% (A/L) from low non-clinically significant to normal were seen.

ALT, total bilirubin and creatinine were measured at all centres. AST, GGT, alkaline phosphatase, direct bilirubin, total protein, urea nitrogen, glucose and albumin were measured only in Burkina Faso, Kenya and Zambia. Direct bilirubin was raised at baseline (in 4.7% and 5.1% per group) but within normal limits by Day 42 and was probably due to haemolysis associated with malaria. The proportions with raised bilirubin fell to 2.3% in both groups by the end of the study

Safety related to drug-drug interactions and other interactions

DM 040010

Paracetamol was taken by 66% and 68% of patients in the two groups. One quarter of all patients was taking vitamin B-complex, one third received dextrose and sodium chloride and about one quarter received a glucose injection.

DM 040011

Paracetamol was taken by 83% and 82% per group. Over half of all patients took an antibacterial agent during the trial with amoxicillin prescribed most often (44% and 46%). Ferrous sulfate was prescribed for anaemia associated with malaria in 15% per group.

Discontinuation due to adverse events

DM 040010

Four patients in the DHA/PQP group and one in the AS+MQ group stopped treatment prematurely due to AEs. All AEs resolved completely. The table does not show all discontinuations from study

Table 66: Significant Adverse Events Causing Early Discontinuation of Study Treatment (Safety Population)

| Patient No. | Age (Years) | Sex | Preferred Term | Onset Day | End Day | Severity | Serious | Relation to Treatment |
|----------------|-------------|--------|----------------------|-----------|---------|----------|---------|-----------------------|
| DHA/PQP | | | | | | | | |
| 20-211-4186 | 3 | Female | Vomiting | 2 | 2 | Severe | No | Possible |
| 20-215-4190 | 3 | Female | Vomiting | 2 | 2 | Severe | No | Possible |
| 22-132-2700 | 28 | Male | Nausea | 2 | 3 | Severe | No | Unrelated |
| 43-052-3850 | 38 | Male | Grand Mal Convulsion | 0 | 0 | Severe | Yes | Possible |
| AS+MQ | | | | | | | | |
| 22-020-2588 | 20 | Male | Vomiting | 0 | 3 | Severe | No | Unrelated |

DM 040011

Five patients in Kenya in the DHA/PQP group stopped treatment prematurely due to AEs. None of these AEs was serious and all resolved completely. One patient took Malarone for *P. falciparum* malaria on Days 2-4 and Claritin for the skin reaction and pruritus on Days 2-6. Another took Malarone for *P. falciparum* malaria on Days 2-4, paracetamol on Days 1-3 and Piriton for the skin reaction on Days 2-5 and one other took Piriton for allergic dermatitis on Days 2- 6. There was no history of chloroquine use by these three patients. There were no early discontinuations in the A/L group at any centre.

Table 67: Significant Adverse Events Causing Early Discontinuation of DHA/PQP (Safety Population)

| Patient No. | Age (months) | Sex | Preferred Term | Onset Day | End Day | Severity | Relation to DHA/PQP |
|-------------|--------------|--------|---------------------|-----------|---------|----------|---------------------|
| 32-023-473 | 13 | Female | Vomiting | 0 | 1 | Moderate | Possible |
| 32-125-570 | 13 | Male | Vomiting | 0 | 0 | Mild | Possible |
| 32-141-586 | 52 | Male | Skin Reaction | 2 | 5 | Mild | Probable |
| | | | Pruritus | 2 | 3 | Mild | Possible |
| 32-198-641 | 36 | Female | Skin Reaction | 1 | 3 | Mild | Possible |
| 32-204-645 | 8 | Female | Dermatitis Allergic | 2 | 4 | Mild | Possible |

Post marketing experience

No post-marketing data with Eurartesim are available. However, a short summary of the postmarketing experience from similar combination drugs Artekin and DuoCotexim was provided.

Meta-analysis on safety of PQP

A meta-analysis on safety of PQP derived from published literature, compared the number of deaths which occurred in 55 clinical trials in patients treated with PQP alone or in combination with any other compound(s). In total 19,446 patients treated with DHA/PQP were considered (9,015 in controlled studies and 561 in uncontrolled studies for the treatment of uncomplicated malaria, 192 in PK studies and 9,678 in IPT studies). The results demonstrate no excess of risk of dying in the DHA/PQP group as compared with all other considered treatment groups. However, due to several deficiencies, this meta-analysis cannot rule out the possibility of differences between the different antimalarials.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The safety database for Eurartesim consists of exposure to subjects enrolled in clinical studies sponsored by the applicant and included 1862 adult and paediatric patients with malaria. Most data are derived from the pivotal trials DM 040010 and DM 040011. Overall, Eurartesim treatment was well tolerated in the studied patient populations. As an important TEAE, QTc prolongation was identified. The QTc prolongation was asymptomatic in all cases and was not associated with more clinically significant abnormalities. The applicant provided a meta-analysis of safety of piperaquine derived from

published papers that did not suggest an excess risk of death for Eurartesim vs. other antimalarial agents. However, this meta-analysis cannot rule out the possibility of an excess risk.

In the Asian study, analysis of rates of all cardiac AEs and drug-related cardiac AEs in the DHA/PQP group of arrhythmic nature (sinus bradycardia, sinus tachycardia and sinus arrhythmia) showed that these were more frequent in the DHA/PQP group than AS+MQ group. However, all drug-related events of arrhythmic nature were considered mild, not serious and occurred without concomitant cardiovascular events.

The limitations of the safety database were influenced by eligibility criteria used in pivotal trials

The trials did not include elderly patients, pregnant or lactating women and patients with moderate or severe liver or moderate to severe renal diseases.

The follow up of patients in the Phase III studies was too short to allow detection of long-term adverse reactions.

Additional expert consultations

During the MA application, an Ad-Hoc Expert Committee was convened to discuss cardiac safety aspects of Eurartesim. The questions posed to experts were as follows:

- The possible risk of cardiac arrhythmia secondary to QTc prolongation even when Eurartesim is administered in the fasting state
- The possible effect of administration in the fasting state on efficacy
- In light of their findings on these issues, the advisory group is requested to comment on the possible role of Eurartesim in the management of acute uncomplicated falciparum malaria in the EU

Overall, the experts advised that the significant QTc prolongation observed with Eurartesim administration poses a problem and unpredictable risk for a small proportion of people. However, they were reassured by the data when Eurartesim was administered in the fasting state and by the clinical data that are available so far.

The data on efficacy whilst fasting were reassuring and permit recommendation for administration of Eurartesim between meals.

Overall, Eurartesim would increase the available therapeutic armamentarium. It provides an additional choice in treating uncomplicated falciparum malaria.

2.6.2. Conclusions on clinical safety

In clinical trials, Eurartesim was generally safe and well tolerated.

Treatment emergent QTc prolongation was asymptomatic in all cases. The magnitude of QTc prolongation is reduced if dosing occurs between meals. The potential concern that the QTc prolongation might lead to serious cardiac arrhythmias is addressed appropriately in the approved RMP.

Limitations of the safety database include missing information on categories of patients belonging to the target population. This shortcoming is reflected in the Product Information as stated in sections 4.3 or 4.4 of the SmPC and in the RMP.

The CHMP considers the following measures necessary to address issues related to safety:

To further substantiate the cardiac safety of Eurartesim use in patients with signs and symptoms of uncomplicated malaria, including the effect of Eurartesim administration on QTc intervals, the MAH shall provide the results of an epidemiological study addressing this issue, according to a CHMP agreed protocol.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Table 68: Summary of the risk management plan

| Safety concerns | Agreed pharmacovigilance activities | Agreed risk minimisation activities |
|---|--|--|
| Identified risk: | | |
| <p>QTc prolongation</p> <p>Food interaction</p> | <p>Routine PV, special monitoring of cardiovascular AEs including QTc prolongation:</p> <ol style="list-style-type: none"> 1. In-depth revision and analysis of individual AE reports; 2. In-depth revision and analysis of aggregated data during the periodic "Safety Surveillance Meeting" performed quarterly by the Applicant's Corporate Safety Department, in order to monitor the identified risks; 3. In addition, these cases will be presented and discussed in the PSUR section "Overall Safety Evaluation" with additional reference from section "Analysis of individual case histories". <p>Additional PV activities: For cases of reported QT prolongation or events, possibly related to QT prolongation and cardiac arrhythmia, ST have designed a specific questionnaire to get as much follow-up information as possible on these cases.</p> <p>The Applicant commits to performing a registry study in the European Union, aiming at assessing the incidence of treatment-emergent adverse events of special interest (torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, seizures and sustained arrhythmias), co-morbidities and concomitant medications, as well as at monitoring patterns of drug utilization.</p> | <p>Routine risk minimisation activities: Patients at increased risk for arrhythmias are described in Section 4.3 'Contraindications' and 4.4 'Special warnings and precautions for use' of the SPC and in Section 4.5 'Interaction with other medicinal products and other forms of interactions'.</p> <p>The SPC was amended to reflect the new findings from the food interaction studies: Eurartesim should only be taken with water and without food. Each dose should be taken no less than 3 hours after the last food intake. No food should be taken within 3 hours after each dose.</p> <p>Additional risk minimization activities: An Educational Guide for HCPs will describe the identified risk of QTc prolongation highlighting the need to take Eurartesim with water and without food. Each dose should be taken no less than 3 hours after the last food intake. No food should be taken within 3 hours after each dose.</p> <p>The recommendations for ECG monitoring and a warning of possible interactions. A checklist for contraindicated conditions for use and contraindicated concomitant medications (drugs known to prolong the QTc interval) will be included in the educational material provided to HCPs. Patients will be advised to contact their doctor about adverse events, and</p> |

| | | |
|-------------------------|--|--|
| | <p>Once Eurartesim is registered in Africa, the applicant intends to participate in the large epidemiologic INESS (INDEPTH Effectiveness and Safety Studies) study to monitor the effectiveness/safety of DHA/PQP when used for treatment of uncomplicated <i>P. falciparum</i> malaria in endemic countries. The INESS study is a spontaneous observational study, which will include 10,000 patients with uncomplicated malaria and a sub-set of 1,000 patients with prospective ECG monitoring.</p> | <p>specifically any alterations in cardiac rhythm or symptoms (e.g. loss of consciousness). The Patient Information Leaflet will include a list of adverse events potentially associated with QT prolongation.</p> <p>Details of the registry (e.g. contact data for each country) will also be included with the educational material, in the countries where the registry will be run.</p> |
| Potential risks: | | |
| Neurotoxicity | <p>Routine PV, including surveillance of AEs regarding Neurotoxicity:</p> <ol style="list-style-type: none"> 1. In-depth analysis of individual AE reports; 2. Revision and analysis of aggregated data during the periodic "Safety Surveillance Meeting" performed quarterly by the Applicant's Corporate Safety Department, in order to identify potential risks; 3. In addition, these cases will be presented and discussed in the PSUR section "Overall Safety Evaluation" with additional reference from section "Analysis of individual case histories". <p>Monitor potential convulsions as part of INESS epidemiologic study of DHA/PQP in treatment of uncomplicated <i>P. falciparum</i> malaria in endemic countries.</p> | <p>Section 4.8 of the SPC 'Undesirable Effects' lists 'Convulsion' as an Uncommon ADR in Eurartesim clinical trials in both adult and paediatric patients.</p> <p>Section 5.3 of the SPC 'Preclinical Safety Data' advises that the potential for neurotoxicity of orally administered DHA in humans can be considered highly unlikely, given the rapid clearance of DHA and its short exposure (3 days of treatment for malaria patients). There was no evidence of DHA-induced lesions in the specific nuclei in rats or dogs, even at lethal dose.</p> |
| Phototoxicity | <p>Routine PV, including surveillance of AEs regarding Phototoxicity:</p> <ol style="list-style-type: none"> 1. In-depth analysis of individual AE reports; 2. Revision and analysis of aggregated data during the periodic "Safety Surveillance Meeting" performed quarterly by the Applicant's Corporate Safety Department, in order to identify potential risks; 3. In addition, these cases will be presented and discussed in the PSUR section "Overall Safety Evaluation" with additional reference from section "Analysis of individual case histories". | <p>No risk minimisation activities are proposed at this time.</p> |
| Reproductive toxicity | <p>Routine PV;</p> <p>Two pregnancy registries are planned by the Applicant: one in the European Union (A European multi-centre pregnancy Registry for patients exposed to Eurartesim™ for the treatment of malaria whilst pregnant), and another in Africa (Assessment of the Safety of the Antimalarial Drug use During Early Pregnancy, ASAP);</p> <p>PREGACT study (ITMP0308): Safe and efficacious artemisin-based combination treatments for African pregnant women with malaria.</p> <p>Pharmacokinetics of piperaquine in pregnancy: spontaneous study to define the</p> | <p>Routine risk minimisation activities:</p> <p>Per Section 4.6 'Fertility, pregnancy and lactation' of the SPC, Eurartesim should not be used during pregnancy in situations where other suitable and effective anti-malarials are available.</p> <p>Additional risk minimization activities:</p> <p>An educational outreach program will be conducted - educational materials will be provided to HCPs (HCP Information Pack) outlining the potential risk of reproductive toxicity and the action to take in the event of pregnancy.</p> <p>Details of the pregnancy registry (e.g. contact data for each country) will also be</p> |

| | | |
|---|--|---|
| | pharmacokinetic disposition of PQ in pregnant women; The results of spontaneous studies using Eurartesim will be added. | included with the educational material. |
| Development of resistant Plasmodium strains | Routine PV; Close collaboration with international organizations (including BCRT and WWARN). The collaboration with Berlin Center for Travel & Tropical Medicine (BCRT) consists at present in a preliminary agreement which includes the outline of a protocol of a prospective study aimed to verify the efficacy and safety of Eurartesim in those patients with imported <i>P. falciparum</i> malaria treated at BCRT. The collaboration between the Applicant and the WWARN will be based on the acceptance to transfer the Applicant databases of the Phase 3 clinical studies to WWARN. The rules for this transfer will be defined by June 2011. | No risk minimisation activities are proposed at this time. |
| Missing information: | | |
| Use in children below 6 months of age or below 5kg body weight | Routine PV; A study in infants (1 to 12 months of age) has been agreed upon with the PDCO to assess the safety/tolerability of an age-appropriate formulation. | Routine risk minimisation activities: Children below 6 months were excluded per Section 4.2. of the SPC. In clinical trials children from 6 months onwards were treated with no additional safety concerns detected. |
| Use in pregnant and lactating women | Routine PV; Two pregnancy registries are planned by the Applicant: one in the European Union (A European multi-centre pregnancy Registry for patients exposed to Eurartesim™ for the treatment of malaria whilst pregnant), and another in Africa (Assessment of the Safety of the Antimalarial Drug use During Early Pregnancy, ASAP); PREGACT study (ITMP0308): Safe and efficacious artemisin-based combination treatments for African pregnant women with malaria. Pharmacokinetics of piperaquine in pregnancy: spontaneous study to define the pharmacokinetic disposition of PQ in pregnant women; The results of spontaneous studies using Eurartesim will be added. | Routine risk minimisation activities: Per Section 4.6 'Fertility, pregnancy and lactation' in the SPC, Eurartesim should not be used during pregnancy in situations where other suitable and effective anti-malarials are available. Additional risk minimization activities: An educational outreach program will be conducted - educational materials will be provided to HCPs (HCP Information Pack) outlining the potential risk of reproductive toxicity and the action to take in the event of pregnancy. Details of the registry will also be included. |
| Use in patients with moderate/severe renal or moderate/severe hepatic impairment Use in patients with cardiac impairment | Routine PV, including surveillance of AEs in Special Populations: 1. Revision and analysis of aggregated data during the periodic "Safety Surveillance Meeting" performed quarterly by the Applicant's Corporate Safety Department, in order to identify potential risks. 2. In addition, these cases will be presented and discussed in the PSUR section "Overall Safety Evaluation – Special Populations". | Routine risk minimisation activities: Per Section 4.2 'Posology and method of administration' of the SPC, in patients with moderate or severe renal impairment, or moderate or severe hepatic impairment, caution is advised. |
| Use in patients with HIV/AIDS | Routine PV | No risk minimisation activities are proposed at this time. |
| Use in elderly patients - patients >65 years | Routine PV, including AE surveillance in elderly >65 years. | Routine risk minimisation activities: Section 4.2 of the SPC advises that clinical studies of Eurartesim tablets did not include subjects aged 65 years and over. |

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| Use in patients with a BMI > 27 and overweight patients (>100 kg body weight) | Routine PV to capture potential insufficient efficacy in patients with body weight >100 kg. Dose for body weight >100 kg to be established. | Section 4.2 of the SPC 'Posology and method of administration' advises that 'there are no data on which to base a dose recommendation in patients weighing >100kg'. |
| Use in patients of Caucasian Ethnicity | Routine PV. | No risk minimisation activities are proposed at this time. |
| Long-term AE data and repeated use of Eurartesim | Routine PV including surveillance of all AEs. | Per SPC, if more than two malaria infections occur within 12 months, alternative treatment is recommended. If a recurrent parasitaemia occurs within 2 months after the first Eurartesim treatment, an alternative antimalarial treatment is recommended. |
| Drug interaction with CYP3A4 metabolised drugs Drug interaction with other antimalarial drugs | With regard to CYP3A4 substrates, the applicant has agreed to provide Eurartesim to a third party organisation investigating the possibility of pharmacokinetic interactions between artemisinin combination therapies and anti-retroviral drug regimens. Although Sigma Tau will not be the sponsor of this study, it will have access to the results and these will be reported in the first PSUR to be submitted after the data become available. Usage in patients with HIV/AIDs will be kept under review in PSURs as a specific group. The following Drug-Drug Interaction studies are also planned (refer to Annex 3a for synopses): <ul style="list-style-type: none"> • Concomitant administration of Eurartesim and Clarithromycin to assess the effect of this potent CYP3A4 inhibitor on the pharmacokinetics of Eurartesim, particularly on PQ. • Concomitant administration of Eurartesim and Midazolam, to assess the effect of Eurartesim on the pharmacokinetics of this CYP3A4 substrate. • Potential interaction of Eurartesim on the pharmacokinetics of oral contraceptives (ethinyl estradiol/levonorgestrel). | Routine risk minimisation activities: Drug interactions with potent CYP3A4 inhibitors, other CYP3A4 metabolised drugs and other drugs known to increase QTc interval are addressed in Section 4.3, 4.4 and 4.5 of the SPC. Concomitant treatment with other antimalarials is addressed in Section 4.4 of the SPC. |
| Use in patients with severe malaria | Routine PV. | Routine risk minimisation activities: Eurartesim is contraindicated in patients with severe malaria according to WHO definition, SPC Section 4.3. |

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

| Description | Due date |
|---|---|
| <p>A post-marketing multi-centre registry study to be conducted in European Union with the objective to investigate the association between the Eurartesim induced QTc prolongation and possible predictive factors, and estimate the incidence of treatment-emergent adverse events of special interest. The information collected will include data on:</p> <ul style="list-style-type: none"> - possible predictive factors such as age, gender, ethnicity, food intake, co-morbidities and co-medication - adverse events of special interest such as torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, seizures and sustained arrhythmias. <p>The study will also monitor the patterns of drug utilization for Eurartesim.</p> | <p>Progress reports on enrolment and intermediate analysis results will be provided yearly with PSURs Final study report date submission by 31 December 2015</p> |
| <p>An epidemiologic study on the safety of Eurartesim when used patients with signs and symptoms of uncomplicated malaria confirmed by a Rapid Diagnostic Test (RTD) or, when this test is not available, by WHO diagnostic criteria (INESS study). The study will be conducted in demographic sentinel sites investigating at least 10000 malaria cases. A subset of at least 1000 patients will be investigated for the effect of the administration of Eurartesim on blood biochemistry, full blood count and QTc intervals.</p> | <p>Final study report submitted by 31 December 2014</p> |
| <p>A post-marketing registry to be set-up in European countries with the objective to gain additional information on the safety of Eurartesim exposure during pregnancy. The prospective, observational registry study will evaluate the live birth prevalence of minor and major congenital birth defects and shall assess the foetal and maternal outcomes of pregnancy in women who were exposed at any time during pregnancy to Eurartesim for the treatment of malaria.</p> | <p>Yearly reports on patient recruitment, at the time of the PSUR submission. Interim analysis reports every two years, at the time of the PSUR submission. Final study report by December 2018</p> |

The following additional risk minimisation activities were required:

- A healthcare professional educational pack, to be provided to all physicians who are expected to prescribe or use Eurartesim, containing the following:
 - The Summary of Product Characteristics
 - The Patient Information Leaflet
 - The Physician Leaflet including the *Contraindicated Conditions of Use and Contraindicated Concomitant Medication* checklist

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

- The outstanding study protocols for studies included in the EU-RMP pharmacovigilance plan should be submitted for CHMP assessment and approval.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Eurartesim meets the WHO recommendations for ACT since it comprises an artemisinin with a longer-acting partner drug. The two Phase 3 studies have demonstrated acceptable clinical efficacy of Eurartesim for the treatment of uncomplicated falciparum malaria in endemic areas.

Uncertainty in the knowledge about the beneficial effects

The possibility that dosing apart from food as recommended in the SmPC could have a negative impact on efficacy cannot be wholly dismissed. There is no appreciable effect of food on DHA absorption, which affects the early parasitocidal activity, but dosing Eurartesim with food greatly enhances piperaquine plasma levels. In this regard, the timing of the three daily doses in relation to food intake could not be discerned with confidence from the data collected during the Phase 3 clinical studies. While it is likely that the first doses were often taken on an empty stomach due to acute illness, the actual dosing conditions probably changed as clinical recovery ensued so that the second and third doses were more likely to have been taken with or close to a meal.

It is not possible to be sure that the efficacy observed in subjects resident in endemic areas would necessarily apply to returning EU travellers. EU travellers will comprise a mixture of ethnicities and a proportion of EU residents who spent much of their early life in endemic areas may still have some residual immunity to malaria but the majority will not. Plasma exposure to DHA and to PQP was at least numerically higher in healthy Asians vs. Caucasian subjects and was higher for DHA in female vs. male subjects on dosing after a light meal. However, the plasma levels of DHA are clearly very different between subjects with acute malaria and healthy subjects, which makes it difficult to draw any conclusions from these observations.

Risks

Unfavourable effects

With the exception of effects on QTc intervals, the types and rates of unfavourable effects documented in the clinical studies were comparable between Eurartesim and the other ACTs that were evaluated.

Uncertainty in the knowledge about the unfavourable effects

The current safety database is not sufficiently large to determine whether the QTc effect of Eurartesim will translate into arrhythmias and, if so, how frequently these may occur. However, the non-clinical data suggest that, despite the effect on QTc, the torsadogenic potential of Eurartesim may be low and there are currently no clinical data (from sponsored or published studies) that indicate a signal for clinically significant treatment-associated arrhythmias.

Benefit-risk balance

On current evidence, the risk-benefit balance of Eurartesim in treatment of uncomplicated falciparum malaria could be deemed favourable. This position takes into account the risk for cardiac side effects resulting from the pronounced Eurartesim-induced QTc-interval prolongation as demonstrated in the thorough QTc-study as well as in the pivotal clinical studies. It is considered that these safety concerns be sufficiently covered by the precautionary measures stated in the product literature.

Discussion on the benefit-risk balance

Malaria is a global problem with the greatest burden of disease and mortality occurring in tropical countries. Malaria is particularly dangerous in children under 5 years of age, pregnant women and previously unexposed visitors to endemic areas. *P. falciparum* is the most prevalent, treatment resistant form of malaria and is responsible for the severe and most deadly forms of the disease in children and adults.

A substantial number of EU residents are at risk of contracting malaria during leisure or business travel and migration. Eurartesim is an artemisinin-containing combination (ACT) that is recommended by the 2010 WHO guidelines for the treatment of malaria and is currently expected to be active against *P. falciparum* worldwide. In the two Phase 3 studies conducted in Asia (including areas with multiple drug-resistant falciparum strains) and in Africa, Eurartesim showed comparable efficacy to other ACT regimens in residents of endemic areas. However, based on pharmacokinetic data and plasma levels it cannot be ruled out that efficacy might not be quite as good as observed in the Phase 3 studies in subjects with no prior exposure to malaria and when Eurartesim is dosed apart from food.

The sponsored clinical studies indicated that, with the exception of the degree of effect on the QTc interval, the safety profile of Eurartesim was comparable to that of other ACTs. The non-clinical data and the available clinical data do not suggest that the effect on QTc is associated with serious cardiac arrhythmias, including torsades de pointes, but this possibility cannot be dismissed. Hence the SmPC and RMP take into consideration this possibility. In particular, the SmPC includes contraindications, warnings and precautions that are intended to minimise any risk for serious cardiac arrhythmias to occur.

Likewise as for other infective diseases, it is vital for the physician to have multiple treatment options. As such, Eurartesim might offer a useful alternative to current lead treatments available in Europe.

Overall, Eurartesim provides a Europe-wide alternative in the armamentarium of uncomplicated *P. falciparum* malaria treatment. The identified safety concerns are addressed in the Risk Management Plan (RMP) and Annex II.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Eurartesim in the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 11.0 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached at the request of the EMA

The PSUR cycle for the product will follow the standard requirements until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The Marketing Authorisation Holder shall agree the format and content of the physician leaflet with the National Competent Authority prior to launch in the Member State.

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Eurartesim are provided with a healthcare professional educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet

- The Physician Leaflet including the Contraindicated Conditions of Use and Contraindicated Concomitant Medication checklist

The Physician Leaflet should contain the following key messages:

- That Eurartesim has a potential to prolong the QTc interval that may lead to potentially lethal arrhythmias.
- That piperaquine absorption is increased in the presence of food, therefore to reduce this risk of QTc interval prolongation, the patients should be advised to take the tablets with water, without food, no less than three hours after the last food intake. No food should be taken within 3 hours after each dose.
- That Eurartesim is contraindicated in patients with severe malaria according to WHO definition and in patients with a history of clinical conditions that may lead to QTc interval prolongation, and in patients taking drugs that are known to prolong the QTc interval.
- The ECG monitoring recommendations.
- The scope and use of the Contraindicated Conditions of Use and Contraindicated Concomitant Medication checklist
- That there is a potential risk of teratogenicity and so Eurartesim should not be used in situations where other suitable and effective anti-malarials are available.
- The need to counsel patients on important risks associated with Eurartesim therapy and appropriate precautions when using the medicine.
- That patients should be advised to contact their doctor about adverse events and that physicians/pharmacists should report suspected adverse reactions to Eurartesim, and in particular, those associated with a QT prolongation.
- The existence and scope of the pregnancy register and details of how to enter patients in it.

In Member States where the EU safety registry will be available, the educational materials should include details on the registry and how to enter patients in it.

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

| Description | Due date |
|--|------------------|
| To further substantiate the cardiac safety of Eurartesim use in patients with signs and symptoms of uncomplicated malaria, including the effect of Eurartesim administration on QTc intervals, the MAH shall provide the results of an epidemiological study addressing this issue, according to a CHMP agreed protocol. | 31 December 2014 |

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

The Member States shall agree the final educational material with the Marketing Authorization Holder (MAH) prior to launch of the product in their territory.

The Member States shall ensure that the MAH provides all physicians who are expected to prescribe or use Eurartesim a healthcare professional educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet
- The Physician Leaflet including the Contraindicated Conditions of Use and Contraindicated *Concomitant Medication* checklist

The Physician Leaflet should contain the following key messages:

- That Eurartesim has a potential to prolong the QTc interval that may lead to potentially lethal arrhythmias.
- That piperaquine absorption is increased in the presence of food, therefore to reduce this risk of QTc interval prolongation, the patients should be advised to take the tablets with water, without food, no less than three hours after the last food intake. No food should be taken within 3 hours after each dose.
- That Eurartesim is contraindicated in patients with severe malaria according to WHO definition and in patients with a history of clinical conditions that may lead to QTc interval prolongation, and in patients taking drugs that are known to prolong the QTc interval.
- The ECG monitoring recommendations.
- The scope and use of the Contraindicated Conditions of Use and Contraindicated Concomitant Medication checklist
- That there is a potential risk of teratogenicity and so Eurartesim should not be used in situations where other suitable and effective anti-malarials are available.
- The need to counsel patients on important risks associated with Eurartesim therapy and appropriate precautions when using the medicine.
- That patients should be advised to contact their doctor about adverse events and that physicians/pharmacists should report suspected adverse reactions to Eurartesim, and in particular, those associated with a QT prolongation.
- The existence and scope of the pregnancy register and details of how to enter patients in it.
- In Member States where the EU safety registry will be available, the educational materials should include details on the registry and how to enter patients in it.

Active substance status

Based on the declaration of the applicant, this medicinal product shall be considered as a new fixed dose combination of active substances.