EMA/CHMP/61768/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pyramax

pyronaridine tetraphosphate / artesunate

Procedure No.: EMEA/H/W/002319

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ACPR	adequate clinical and parasitological response
ACT	artemisinin-based combination therapy
AE	adverse event
Ae	Amount of drug excreted in urine (% recovered of the administered dose)
AL	artemether/lumefantrine
ALT	alanine aminotransferase
AS	artesunate
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
AUC_{0-last}	area under the curve from time 0 to last measurable concentration
CI	confidence interval
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cl	Plasma clearance
C_{max}	Maximal plasma concentration
CV	coefficient of variation
DHA	dihydroartemisinin
ECG	electrocardiogram
EE	efficacy evaluable
ETF	Early Treatment Failure
FCT	Fever clearance time
G-6-PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ITT	intent-to-treat
JP	Japanese Pharmacopoeia
LCF	Late Clinical Failure
LDPE	Low density polyethylene
LPF	Late Parasitological Failure
MIC	minimum inhibitory concentration
MQ	mefloquine
MQ + AS	mefloquine + artesunate
P. berghei	*Plasmodium berghei*
P. falciparum	*Plasmodium falciparum*
P. ovale	*Plasmodium ovale*
P. vivax	*Plasmodium vivax*
PA	pyronaridine tetraphosphate/artesunate
Ph. Eur.	European Pharmacopoeia
Ph. Int.	International Pharmacopoeia
PCR	polymerase chain reaction
PCT	parasite clearance time
PD	pharmacodynamics
PIP	paediatric information plan
PK	pharmacokinetics
PP	pyronaridine tetraphosphate
QTc_B	QT using Bazett correction
QTc_{Frid}	QT using Fridericia correction
$t_{1/2}$	(elimination) half-life
$t_{1/2\beta}$	terminal half-life
t_{max}	time to maximal (peak) plasma or blood concentration
TBM	"to-be-marketed"
TRS	Technical report series
URTI	upper respiratory tract infection
SAE	serious adverse event
SAP	Statistical Analysis Plan
V2/F	volume of distribution in central compartment (pyronaridine population

	pharmacokinetics) or volume of distribution (AS/DHA population pharmacokinetics)
V3/F	volume of distribution in peripheral compartment (pyronaridine population pharmacokinetics) or in central compartment (AS/DHA population pharmacokinetics)
V4/F	volume of distribution in peripheral compartment (AS/DHA population pharmacokinetics)
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shin Poong Pharmaceutical Co., Ltd. submitted on 9 April 2010 an application in accordance with Article 58 of Regulation (EC) No 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organisation for Pyramax.

The eligibility by the World Health Organisation was agreed upon on 2 June 2006.

Pyramax will be intended exclusively for markets outside the Community.

The applicant applied for the following indication:

"Pyramax is a fixed dose combination of pyronaridine tetraphosphate and artesunate which acts as a blood schizonticide on *Plasmodium falciparum* and *Plasmodium vivax* malaria.

Treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in patients weighing 15 kg or more.

Pyramax is effective against drug susceptible and drug resistant *Plasmodium falciparum* malaria and can be used to treat patients where resistance to other agents is known."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application, by analogy to the European Legislation

The application submitted is for a fixed combination medicinal product 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 tests or studies.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Not applicable.

New active Substance status

Not applicable.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

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: Philippe Lechat Co-Rapporteur: Barbara van Zwieten-Boot

- The application was received by the EMA on 9 April 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 August 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2010.
- During the meeting on 20-23 September 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 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 9 July 2011.
- During the CHMP meeting on 18-21 July 2011, 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 List of Outstanding Issues on 18 October 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the list of outstanding issues to all CHMP members on 1 December 2011.
- During a meeting of an Expert group on 9 December 2011, experts were convened to address questions raised by the CHMP.
- The CHMP agreed on remaining outstanding issues via written procedure on 9 January 2012.
- During the CHMP meeting on 16-19 January 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The applicant submitted the responses to the remaining outstanding issues on 18 January 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the remaining outstanding issues on 6 February 2012.
- During the meeting on 13-16 February 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Pyramax on 16 February 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

Malaria is a significant global health challenge affecting mainly young children and pregnant women. The World Health Organization (WHO) estimates that there are 300 – 500 million clinical cases of malaria each year, 90 % of which are in Africa. There are between 1.5 and 2.7 million deaths annually and at least 1 million of the deaths are African children under 5 years of age. *Plasmodium falciparum* (*P. falciparum*) and *Plasmodium vivax* (*P. vivax*) account for the majority of cases, with *P. falciparum* being the species causing substantial morbidity and the majority of the mortality. *P. vivax* infection is rarely life-threatening, but is responsible for important morbidity especially in young children that are the most vulnerable to severe outcome. *P. vivax* forms persistent hypnozoite parasite stages in the liver that can result in multiple relapses of infection weeks to months after the primary infection.

The widespread resistance of *P. falciparum* has rendered conventional monotherapies such as chloroquine (CQ), amodiaquine, and sulfadoxine/pyrimethamine less effective. Resistance is an increasing problem in the treatment of malaria.

Given the risk in the development of resistance to antimalarial agents, the WHO generally recommends that new antimalarial medicines for use at public health level have an average cure rate >95% as assessed in clinical trials. Moreover, WHO consider that the change of an antimalarial medicine recommended in the additional malaria treatment policy should be initiated if the total treatment failure proportion is ≥ 10% as assessed through *in vivo* monitoring of therapeutic efficacy (WHO, 2010).

Artemisinin derivatives are widely used anti-malarial medicines, clearing parasites rapidly. Artemisinins are recommended by WHO to be given in combination with another anti-malarial agent with a longer half-life in order to prevent the occurrence of drug resistance to artemisinins and to compensate for their relatively short half-life. Accordingly, artemisinin-based combination therapies (ACTs) have been increasingly used in endemic area to treat uncomplicated *P. falciparum* malaria. Published data refer to their benefit in slowing or even reversing the emergence of parasite resistance in endemic countries.

According to WHO recommendation, when administered with rapidly eliminated compounds (e.g. tetracyclines, clindamycin), a 7-day course of combination therapy is required. When administered with a more slowly eliminated anti-malarial drug (e.g. lumefantrine), a shorter 3-day course of treatment can be efficiently used. The objective of a 3-day course ACT treatment is to act over 2 asexual cycles to substantially reduce parasite numbers, ensuring a rapid clinical response and, in the same time, improving compliance to treatment.

The present application seeks for a scientific opinion by CHMP in the scope of Article 58 of Regulation (EC) No 726/2004, for the artemisinin-based combination therapy (ACT): pyronaridine tetraphosphate 180 mg/ artesunate 60 mg, Film-coated tablets.

Artesunate (AS) is the most widely used member of the artemisinin derivative drugs in endemic area.

As single agent, pyronaridine has been used in China for over 30 years; initial clinical trials were conducted in China. Pyronaridine (the tetraphosphate) is listed in Chinese Pharmacopeia and was also available in certain regions of China in oral tablet forms or as parenteral injection.

Pyronaridine is proposed by Shin Poong Pharmaceutical Company due to its intermediate half life as a partner drug for artesunate in a 3-day regimen for the treatment of uncomplicated malaria infection caused by *P. falciparum* or *P. vivax*.

About the product

Pyramax 180/60 mg Film-coated tablet is a fixed dose combination of pyronaridine tetraphosphate 180 mg and artesunate 60 mg.

Proposed indication (from the applicant at submission):

The therapeutic indication **initially** claimed by the applicant was:

"Pyramax is a fixed dose combination of pyronaridine tetraphosphate and artesunate which acts as a blood schizonticide on Plasmodium falciparum and Plasmodium vivax malaria.

Pyramax tablets are indicated for the treatment of acute, uncomplicated malaria infection caused by Plasmodium falciparum or by Plasmodium vivax in patients weighing 15 kg or more.

Pyramax is effective against drug susceptible and drug resistant Plasmodium falciparum malaria and can be used to treat patients where resistance to other agents is known."

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

The dose should be taken orally once a day for three days. Pyramax tablets can be administered with or without food.

In the event of vomiting within 30 minutes of administration after the first dose, a repeat dose should be given. If the repeat dose is vomited, the patient should be given an alternative antimalarial.

In the event of diarrhoea normal dosing should be continued.

Dosage in adults and children

Pyramax tablets should be taken orally as a single daily dose for three consecutive days.

As treatment should be adapted according to body weight, the applicant **initially** proposed the following regimen:

15 - < 24 kg	1 tablet	Daily for 3 days
24 - <45 kg	2 tablets	Daily for 3 days
45 - < 65 kg	3 tablets	Daily for 3 days
≥ 65 kg	4 tablets	Daily for 3 days

Dosage in paediatrics

Pyramax is dosed according to body weight and is suitable for children in the weight categories shown above. Pyramax tablets are not recommended for use in children below 15 kg body weight as safety and efficacy of Pyramax in children below 15 kg has not been established for the tablets.

Dosage in the elderly

There is no experience in elderly patients.

No dosing adjustments would be necessary based on present knowledge and the short 3 day course of treatment.

Dosage in Hepatic impairment

There is no experience in patients with hepatic impairment.

No special precautions or dosage adjustment are anticipated because of the short 3 day course of treatment.

Dosage in Renal impairment

There is no experience in patients with renal impairment.

No special precautions or dosage adjustments are required because of the short 3 day course of treatment.

2.2. Quality aspects

2.2.1. Introduction

Pyramax is presented as orange film coated tablets containing a fixed dose combination of artesunate (60 mg) and pyronaridine tetraphosphate (180 mg). Other ingredients are defined in the SmPC, section 6.1. As Pyramax will be marketed mainly in hot and humid zones, a Tropical blister pack is proposed as container-closure system that is constituted of PVC thermoformed blister with aluminium lidding foil and a second layer (tropical foil) composed of aluminium strip and oPA film heat sealed to the PVC.

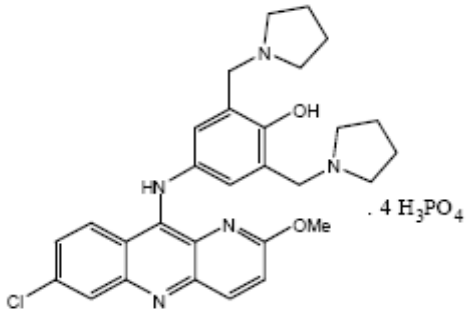
2.2.2. Active Substance

The medicinal product contains two active substances; their scientific discussion will be presented individually below.

Pyronaridine tetraphosphate

Pyronaridine tetraphosphate is referenced in the literature as a synthetic antimalarial that has been first synthesised in 1970. The molecule also called "malaridine" has been in clinical use in China since 1980s. Pyronaridine is not described in Ph. Eur., USP, JP or Ph. Int. It is described in the Chinese Pharmacopoeia under the name malaridine phosphate.

The International Non-proprietary Name (INN) is pyronaridine tetraphosphate. The chemical name of Pyronaridine tetraphosphate is 4-[(7-Chloro-2-methoxybenzo[b]-1,5-naphthyridin-10-yl)amino]-2,6,-bis(1-pyrrolidinylmethyl)phenol tetraphosphate. The molecular formula is $C_{29}H_{32}ClN_5O_2.4H_3PO_4$, its molecular weight: 910.03 and has the following chemical structure:



Pyronaridine tetraphosphate appears as a yellow or orange yellow powder and is freely soluble in water, sparingly soluble in dimethylsulphoxide, very slightly soluble in methanol, practically insoluble in ethanol, dichloromethane and acetone. The molecule does not contain any asymmetric carbon and therefore does not exhibit stereoisomerism. Pyronaridine tetraphosphate does not show polymorphism.

Manufacture

Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the main dossier. The synthetic process consists of 4 steps. All manufacturing steps are adequately described. Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterized.

Specification

The active substance is tested as per in-house specifications. The active substance specifications include tests as: appearance, identification (IR, HPLC, phosphate test), loss on drying, related substances (HPLC), assay (HPLC), residual solvents (GC). The specifications and tests proposed are compliant with the relevant guidelines and are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analyses have been provided for over ten batches. All batches were in compliance with the predefined active substance specifications and confirm consistency and uniformity of the active substance manufacture.

Stability

Pyronaridine tetraphosphate is packaged in LDPE bags, then placed within an aluminium bag and stored in fibre drum. Satisfactory specifications of the packaging components are provided.

Stability studies have been performed on three batches according to ICH guidelines, i.e. long term stability study at 25 °C / 60 % RH (up to three years) and accelerated 40 °C / 75 % RH (6 months). Samples were packed in a container closure system simulating the commercial packaging. The specifications for the stability study include appearance, phosphoric acid assay, related substances with individual maximum impurity and total, loss on drying and assay on dried basis; the limits and tests are those described for batch release.

Additional stress studies have been performed on one batch of pyronaridine tetraphosphate. The study evaluated the following conditions:

High temperature (105 °C for 22 days);

High humidity (25 °C / 80 % RH for 22 days);

Oxidation (6 % hydrogen peroxide at 25 °C for 4 and 24 h);

Acid conditions (0.1 M hydrochloric acid at 25 °C for 22 days);

Alkaline conditions (0.1 M sodium hydroxide solution for 9 days);

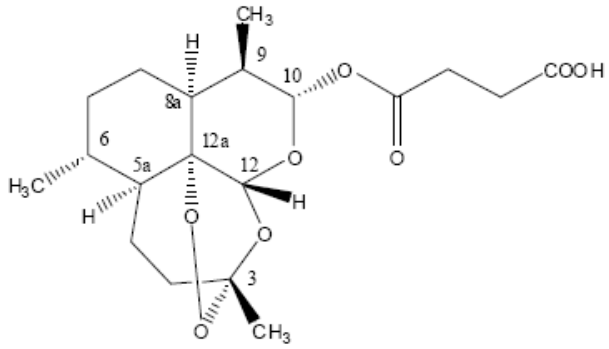
UV light (6 K LUX / h for 22 days).

The stability results support a retest period of 36 months with a precaution storage of "do not store above 25 °C" according to WHO stability guideline.

Artesunate

Artesunate is a known antimalarial described in the Ph. Int. Artesunate is not described in Ph. Eur. or USP. Artesunate is a semi-synthetic compound extracted from *Artemisia annua* leaves.

The International Non-proprietary Name (INN) is artesunate. The chemical name of artesunate is (3R, 5aS, 6R, 8aS, 9R, 10S, 12R, 12aR)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-ol, hydrogen succinate, or [3R-(3, 5, 6, 8, 9, 10, 12, 12R)]-Butanedioic acid mono (decahydro-3,6,9-trimethyl-3,12-epxoy-12H-pyrano-[4,3-j]-1,2-benzodioxepin-10-yl) ester, or Butanedioic acid mono [(3R, 5aS, 6R, 8aS, 9R, 10S, 12R, 12aR)-decahydro 3,6,9 trimethyl-3,12-epoxy-12H-pyrano-[4,3-j]-1,2-benzodioxepin-10-yl] ester. The molecular formula is $C_{19}H_{28}O_8$, its molecular weight: 384.4 and has the following chemical structure:



Artesunate appears as a fine white crystalline powder and is very slightly soluble in water, very soluble in dichloromethane and freely soluble in ethanol and acetone. The molecule contains 8 asymmetric centres and is obtained as the 10α (10S) epimer.

Manufacture

Detailed information about harvesting the plant (inline with WHO guidance), manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the main dossier. The synthetic process from artemisinin consists of 3 steps. In the last step, crude artesunate is purified through a several stage process. All manufacturing steps are adequately described. Satisfactory in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterized.

Specification

The in-house specifications proposed by the applicant are a mixture of Ph. Int. and in-house tests and limits. The active substance specifications include tests as: appearance, identification (IR, colorimetric test), specific optical rotation, sulphated ash, loss on drying, related substances (HPLC), assay (HPLC), residual solvents (GC) and particle size distribution. The specifications and tests proposed are compliant with the relevant guidelines and are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analyses have been provided for over ten batches. All batches were in compliance with the predefined active substance specifications and confirm consistency and uniformity of the active substance manufacture.

Stability

Artesunate is packed in LDPE bag which is placed in an aluminium bag and the whole stored in a fibre drum. Satisfactory specifications are presented for LDPE bag in contact with artesunate, for aluminium bag and for the fibre drum.

Stability studies have been performed on six batches according to ICH guidelines, i.e. long term stability study at 25 °C / 60 % RH (up to three years) and accelerated 40 °C / 75 % RH (up to 6 months). Samples were packed in a container closure system simulating the commercial packaging. The specifications for the stability study include appearance, specific rotation, related substances, loss on drying, pH and assay; the limits and tests are those described for batch release.

Additional stress studies have been performed on one batch of artesunate. The conditions studied are as follows:

- Heat: 65 °C during 20 days;
- Exposure to 80 % humidity during 20 days;
- Exposure to UV light (1watt/h) for 20 days and visible light (6K Lux/h) for 20 days in solid state;
- Oxidation: aqueous solution with 35 % hydrogen peroxide during 13 days;
- Acidic condition: aqueous solution of artesunate treated with 1.0 M HCl during one day;
- Alkaline condition: aqueous solution of artesunate treated with 0.1 M sodium hydroxide during 13 days.

The stability results support a retest period of 36 months with a precaution storage of "do not store above 25 °C" according to WHO stability guideline.

2.2.3. Finished Medicinal Product

Pyramax tablets are orange film coated tablets containing a fixed dose combination of artesunate (60 mg) and pyronaridine tetraphosphate (180 mg) packed in the so called "tropical" blister packs. Each tropical blister will contain 9 tablets and 1 or 10 blisters will be inserted in a paper carton. The "tropical" blister consists in a thermoformed PVC film with an aluminium lid foil on the bottom side and an aluminium cold-formed laminate on the upper side.

Pharmaceutical Development

The aim of the pharmaceutical development was to minimise any contact between the two active substances in order to improve the stability and dissolution profile of the finished product.

The pharmaceutical development is presented in sufficient detail and is supported by adequate amount of experimental data. Adequately designed and reported comprehensive validation studies are presented. Steps in formulations development and manufacturing process development are logical and consistent.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The description of manufacturing process and process controls is presented in sufficient detail and process flow diagram is presented with indication of the critical steps.

Process validation results of three production scale batches were provided. Results of tested parameters are batch to batch comparable and are within proposed limits. The results verify that the process assures adequate batch to batch consistency.

Product specification

The specification of the drug product are acceptable and include: appearance, assay of both active substances (HPLC), uniformity of dosage units, identification by HPLC, UV, or colorimetric test, related substances (HPLC), dissolution, microbiological purity. The finished product specifications are adequate for controlling this pharmaceutical form. The proposed test procedures are adequate. All tests included in the specification have been satisfactorily described and validated.

Certificates of analysis of four production scale batches are provided. The batch analysis results show that the finished product meets the proposed specifications and confirm the consistency & uniformity of manufacture indicating that the process is under control.

Stability of the product

Pyramax tablets will be marketed in hot and humid countries mainly located in climate zones IV a and b according to WHO classification. To protect the tablets from environmental conditions such as high humidity, Pyramax tablets are proposed to be packaged in so called "tropical" blister packs. Each tropical blister will contain 9 tablets and 1 or 10 blisters will be inserted in a paper carton. The "tropical" blister consists of a thermoformed PVC film with an aluminium lid foil on the bottom side and an aluminium cold-formed laminate on the upper side.

The conditions used in the stability studies are in accordance with the ICH and WHO stability guidelines (30 °C/ 65 % RH, 30 °C/ 75 % RH and 40 °C/ 75 % RH) and the packaging similar to that proposed for the market. The control tests and specifications of drug product are adequately drawn up; the attributes monitored during the stability study were appearance, dissolution of each active, artesunate and pyronaridine related substances, assay of each active substance, uniformity of dosage units and microbiological contamination. Based on the stability data provided the proposed shelf-life of 24 months can be granted. The precaution storage to be applied will be "do not store above 30 °C" according to WHO recommendations.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substances and drug product 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 product should have a satisfactory and uniform performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

GLP

Pharmacokinetics studies were not performed in line with GLP rules, except those aiming at investigating the tissue distribution / excretion of PNDP and its metabolism.

The GLP inspection conducted by the US-FDA revealed many discrepancies, e.g. lack of documentation, justification of actions/modification of raw data or lack of equipment calibration/standardization - this further supports the remaining concerns regarding the methods of analysis. Consequently, these studies are not considered fully compliant with GLP requirements. The test facility management acknowledges the observations made and corrective actions were proposed.

The determination of blood levels of pyronaridine and plasma levels of artesunate and dihydroartemisinin (DHA) in samples collected in pivotal 4-week (4-cycles) studies in rats and dogs (studies no. DFF1005 and DFF1006), in mouse micronucleus assays (study no.CPK0303), in the rat liver UDS test (study no.1182801), and in toxicokinetic investigations in pregnant rats and rabbits (studies no.G03149 and G03030) were performed at the clinical pharmacokinetics Laboratory of the University of Iowa (Iowa City, USA).

2.3.2. Pharmacology

For Pyramax or its components no formal development program was undertaken. The assessment of the non-clinical pharmacodynamic effects of Pyramax and its individual components is mainly based on available literature given by the applicant. In addition, two studies evaluating the primary pharmacodynamic effects of Pyramax were performed and a battery of safety pharmacology studies was performed.

Primary pharmacodynamic studies

Pyronaridine tetraphosphate, artemisinin and derivatives of artemisinin have been used in China for the treatment of malaria for more than 30 years. The published literature and the two additional studies performed by the applicant, describe the pharmacodynamic effects of both the individual medicinal components as well as the combination pyronaridine tetraphosphate:artesunate given in a 180:60 mg:mg ratio. Artesunate is a semi-synthetic derivative of artemisinin. *In vivo*, it is rapidly

converted to dihydroartemisinin, the active metabolite. The published literature mainly focuses on dihydroartemisinin and other derivatives of artemisinin.

In vitro, the individual components (pyronaridine tetraphosphate, artemisinin and the derivatives of artemisinin) showed potent activity against *P. falciparum* and *P. vivax* strains and clinical isolates including those resistant to other antimalarials. Activity was greatest for the ring-form stages of the parasite. Similarly, *in vivo*, the individual components exhibited schizonticidal activity in rodent and non-human primate models of malaria and were also efficacious against resistant plasmodium strains. However, recrudescence has been observed following treatment with pyronaridine tetraphosphate and artemisinin alone. Compared to artemisinin, its derivates were more efficacious against both drug-susceptible and –resistant malaria strains. Development of pyronaridine tetraphosphate-resistance against *P. falciparum* following monotherapy with pyronaridine tetraphosphate has been described. However, when used in combination with other antimalarials development of resistance was prevented or significantly retarded. True resistance to artemisinin has not been widely documented, but is of concern. Hence, the combination of pyronaridine tetraphosphate and artemisinin might be efficacious in countering the threat of resistance to *P. falciparum*. The applicant describes the pharmacodynamic effects of the combination pyronaridine tetraphosphate given in a 3:1 ratio. According to the applicant this ratio is based on existing clinical data and current dose levels of pyronaridine and artesunate used in man. No additional studies evaluating the efficacy of this ratio in relation to other ratios have been performed. Based on different mechanisms of action of pyronaridine tetraphosphate (inhibition of haematin formation, which prevents the malarial parasite from neutralizing haem that is toxic to the parasite) and artesunate (generation of free radicals and inhibition of the parasites sarcoplasmic endoplasmatic reticulum calcium-ATPase) the combination might show additive or synergistic potency. The rapid onset of action of artemisinin and its derivatives and the prolonged action of pyronaridine tetraphosphate might be of potential value in this. *In vitro*, contrasting results have been found regarding the additive or synergistic effects of the combination pyronaridine tetraphosphate and artesunate against drug sensitive Plasmodium strains. According to the applicant, the discrepancy is caused by the fact that different experimental models and modes of calculations were used. However, *in vivo*, the combination pyronaridine tetraphosphate and artesunate showed an enhanced therapeutic effect when compared with monotherapy and suggested that curative doses of artesunate could be lowered when given in combination with pyronaridine tetraphosphate. Apart from drug sensitive Plasmodium strains, the combination showed enhanced therapeutic effects and restored efficacy against drug resistant Plasmodium strains or impeded selection of resistance to the individual components, suggesting that the combination may have potential in delaying the selection and spread of resistance. Moreover, the combination showed that radical cure and reduction in the rate of recrudescence can be achieved when combination therapy is started as soon as possible after onset of infection and will be continued for 3 days.

In conclusion, although enhanced therapeutic efficacy has been demonstrated, the results do not indicate whether the combination is additive or synergistic. Moreover, one should keep in mind that for the non-clinical evaluation of the antimalarial activity of the combination pyronaridine tetraphosphate and artesunate, surrogate models have been used. The rodent and non-human primate models used were only infected with their species-specific plasmodium strains. It is not documented whether the mechanism of action of these different species-specific plasmodium strains can be compared. Hence, the overall conclusion if the combination pyronaridine tetraphosphate and artesunate is effective for the treatment against *P. falciparum* and *P. vivax* without developing recrudescence or resistance in humans should be based on the results obtained from the clinical studies performed with this combination.

Secondary pharmacodynamic studies

No specific studies evaluating the secondary pharmacodynamic effects of Pyramax or its individual components were conducted. This was endorsed by CHMP.

Safety pharmacology programme

Safety pharmacology studies were performed to examine the potential effects of pyronaridine tetraphosphate and artesunate alone as well as in 3:1 ratio on cardiovascular, respiratory, renal, gastrointestinal and central nervous systems.

Regarding the effects on the cardiovascular system, pyronaridine tetraphosphate was shown to block hERG current in a concentration-related manner at 0.001 µM and above. The IC_{50} amounted to 0.65 µM, corresponding to 337ng/mL expressed as pyronaridine free-base. This is almost 2-times lower than the C_{max} reported for pyronaridine in humans (726 ng/mL). The applicant explains that due to plasma protein binding and uptake by red blood cells, the concentration of pyronaridine available in the systemic circulation is rather 12 ng/mL, a concentration which would produce <5% hERG channel inhibition. This approach is considered theoretical since the protein binding may not be that restrictive, and the heart is in a central pharmacokinetic compartment readily available to drug concentration. Therefore higher possibly active concentrations than the calculated free fractions must be considered. In addition, the active metabolite of artesunate, DHA, was also shown to block hERG tail current with an estimated IC_{50} of 282 µM, corresponding to 80 µg/mL free base plasma level. C_{max} reported in humans after 3 days treatment for DHA (1.2 µg/mL, i.e. 4.2 µM) is well above that reported for the parent compound AS (0.3 µg/mL). This raises even more concerns since DHA blocks approx. 30% of hERG channels at 100 µM, and is moderately bound to plasma proteins. The fact that the maximal concentration of DHA tested by the applicant is 100 µM, as compared to 300 µM for the electrophysiologically "inactive" parent drug is thus questionable. Overall, a potential for QT interval prolongation cannot be excluded for Pyramax, this point should be handled in the clinical setting.

In Purkinje fibres experiments (study 101202 DCC), DHA and pyronaridine both increase (although modestly) APD durations at lower concentration. But a striking shortening of the APD was observed when increasing the drug concentrations, especially for pyronaridine, which means the drugs profoundly interacts with other channels. SmPC section 5.3 has been updated with reference to hERG results.

Langendorff studies were performed with the objective of investigating left ventricular pressure (LVP), left ventricular developed pressure (LVDP), heart rate (HR), double product (DP) and coronary flow rate (CFR) but were not designed to evaluate QT-interval prolongation. Since repolarisation of the action potential uses different mechanisms in rats and humans, these studies did not bring any additional information of the potential for inducing QT-interval prolongation of Pyramax in humans.

In mice, the combination pyronaridine tetraphosphate: artesunate decreased gut motility (750:250 mg/kg), and hexobarbital-induced sleep time was increased with artesunate alone (≥ 250 mg/kg) and in combination (750:250 mg/kg). In rats, each single agent (≥ 100 mg/kg) and the combination (≥ 75:25 mg/kg) decreased gastric acidity and secretion volume, whereas pyronaridine alone produced significant analgesia in the acetic acid writhing test (≥ 300 mg/kg). The effects noted on the renal system of rats with the combination (375:125 mg/kg) were qualitatively the same as those observed with pyronaridine tetraphosphate administered alone (500 mg/kg), *i.e.* decreased urine volume, increased specific gravity and decreased excretion of sodium and chloride. The clinical relevance of these adverse effects is expected to be low, since all effects occurred following exposure to concentrations that highly exceed the human free plasma level of the drugs due to high intracellular presence and extensive plasma protein binding.

Pharmacodynamic drug interactions

No specific study was conducted. A literature review was undertaken for pyronaridine and artesunate.

2.3.3. Pharmacokinetics

The applicant developed LC-MS methods to determine blood or plasma levels of pyronaridine (PND), artesunate, or dihydroartemisinin (DHA). Methods used in the 4-cycle rat and dog, and in the single-cycle dog studies were validated. In other studies, methods were partially validated, but accuracy and precision values are generally similar. Bioanalytical analyses were not conducted under GLP-compliant conditions.

The pharmacokinetics of pyronaridine and artesunate has been investigated following single intravenous and oral administration to rats and/or dogs of both compounds administered separately or in combination. The pharmacokinetic profile of pyronaridine in both species was characterized by high volumes of distribution, low total blood clearances, and high apparent terminal half-lives (2-4 days in rats, 2.5 days in dogs). The blood concentration vs. time curves declined in a multi-exponential manner, which is in line with slow elimination of the drug from tissues where it accumulates. Following oral administration, the oral bioavailability reached 42.5% in rats and 34.5% in dogs. Since artesunate is rapidly metabolised to DHA, pharmacokinetic parameters could only be determined for DHA. In rats dosed orally, systemic exposure to DHA rose in a supra-proportional manner with increasing dose, suggesting saturation of some mechanism of efflux or first-pass metabolism. Consequently, oral bioavailability ranged from 28% at 5 mg/kg to 123% at 50 mg/kg. In dogs dosed at 10 mg/kg, oral bioavailability reached only 7.2%. The terminal half-life ranged from 0.24 to 1.03 hour in rats, and from 0.39 to 0.66 hour in dogs. Oral or intravenous co-administration of pyronaridine tetraphosphate and artesunate (1:1 ratio) induced a 2-fold decrease in systemic exposure to pyronardine in dogs and a decrease in systemic exposure to DHA in rats.

The binding of pyronaridine to human, dog, rat and rabbit plasma proteins was high in all species (92% to 96%). *In vitro* and *in vivo* investigations showed that pyronaridine preferentially associates with erythrocytes. The distribution of pyronaridine was investigated in rats treated orally once with a 60 mg/kg dose with [^{14}C]-pyronaridine tetraphosphate. Distribution of radioactivity was similar in male and female albino rats. Absorption of radioactivity was rapid with levels of radioactivity present in all tissues at 4 h post-dose, with the exception of the brain (male), eye lens and eye humour. This is in line with the high volume of distribution of pyronaridine and limited clearance. Tissue:blood concentrations ratios were higher than 10 at 72 hours post-dose in most of the tissues, and higher than 100 in the spleen, adrenal gland, liver, thyroid gland, pituitary gland and kidney. At 672 hours (28 days) post-dose, the tissue concentrations of drug-related radioactivity remained high. In pigmented rats, binding of drug-related radioactivity to melanin was observed in the eye (choroid layer) with highest levels reported at 1008 hours (42 days) post-dose (final time point). In the mass balance study conducted in dogs, 14.3% and 6.5% of the administered radioactivity remained in the liver 6 and 24 month, respectively, after receiving a single oral 9 mg/kg dose of [^{14}C]-pyronaridine tetraphosphate. The estimated half-life of drug-related radioactivity in the liver is thus estimated at 12,500 hours, meaning that clearance from the liver is very slow. Overall, these results demonstrate that pyronaridine-related radioactivity accumulates in tissues from which it is extremely slowly eliminated.

Overall, these results show a potential for accumulation of pyronaridine in various tissues.

Investigations in pregnant rats and rabbits showed transfer of pyronaridine across the placenta based on the determination of its concentration in amniotic fluid.

Results published in the literature showed that both artesunate and DHA bind moderately (73% to 82%) to plasma proteins, and associate preferentially with erythrocytes. In rats, artesunate-related radioactivity is mainly found in the spleen and in tissues involved in absorption and excretion.

In vitro turnover of [^{14}C] pyronaridine with rat, dog and human liver microsomes was low, with at least 85% of the test substance remaining after incubation for 60 minutes. In total 9 metabolites were observed as radioactivity peaks in human microsomes and all were also observed in rat and dog microsomes. Most metabolites were not identified because of the low metabolic turnover. Based on *in vitro* studies, pyronaridine may be metabolized by CYP1A2, CYP2D6 and CYP3A4. In addition, it is well-known that artesunate is rapidly metabolised to DHA, that is itself subsequently metabolised to DHA-glucuronide (reaction catalysed by UGT1A9 and UGT2B7).

In rats and dogs dosed orally, pyronaridine is mainly excreted in the faeces. Pyronaridine was also shown to be excreted in rat milk (milk/blood ratio = 36%), thus inducing exposure of suckling pups to the test-article (pup blood / maternal blood ratio at 24 hours post-dose ranging from 5 to 7%). Co-administration with artesunate did not influence the exposure of dams and pups to pyronaridine. Published data showed that in rats [^{14}C]-artesunate-derived radioactivity is mainly excreted in the urine and faeces.

In a study with Caco-2 cell monolayers, pyronaridine inhibited P-gp (IC_{50} of 6.9 µM). Published studies also showed that pyronaridine is an inhibitor of P-gp *in vivo*. In Caco-2 cell monolayers, artesunate and DHA were neither substrates nor inhibitors of P-gp, but a published study reports a potential for P-gp inhibition by DHA (IC_{30} of 7.5 µM). Thus, DHA has some P-gp inhibitory potential, which is lower than that of PND (IC_{50} = 6.9 µM). A warning was added to the SmPC to recommend caution in case of co-administration of Pyramax with P-gp substrates. Pyronaridine was shown to have weak, moderate and strong inhibitory effects on CYP3A4, CYP1A2 and CYP2D6, respectively. The applicant acknowledges that the risk related to CYP2D6 inhibition that may be caused by pyronaridine should be further investigated; in the meantime, a warning was added to the SmPC in case of co-administration of Pyramax with drugs solely metabolized by CYP2D6. The applicant was requested also to add a warning regarding co-administration of Pyramax with UGT inducers or inhibitors since UGTs are involved in the metabolism of artesunate.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were performed in rats with pyronaridine tetraphosphate and artesunate, given either alone or in combination (3:1 ratio). Artesunate appeared to be the most toxic compound, whose maximal non lethal dose amounted to 500 mg/kg whether it was administered alone or in combination with pyronaridine tetraphosphate.

Table 1

Species (no/sex/gp), study ID	Test-article	Dose (mg/kg) – Route	LD50	Observed max non-lethal dose	Major findings
Rat (5) G01026	PNDP:AS	0, 187.5:62.5, 375:125, 750:250, 1500:500 Oral route	> 1500:500	1500:500	– ≥750:250: ↓ locomotor activity, diarrhoea, soft stools, decreased body weight gain. Recovery within 3 days post-dose
Rat (5) G01018	PNDP	0, 250, 500, 1000, 2000 Oral route	> 2000	2000	– ≥1000: diarrhoea, soft stools, decreased body weight gain Recovery within 3 days post-dose
Rat (5) G01022	AS	0, 250, 500, 1000, 2000 Oral route	M: 1700 F: 2200	500	**Mortality:** – 1000: 1M on Day 1, 1F on Day 2 – 2000: 1M on Day 1, 1F on Day 2, 1M and 1 F on Day 3, 1 M on Day 6 Symptoms, body weights – ≥1000: ↓ locomotor activity, transient nasal haemorrhage, diarrhoea, soiled perineal region, – ≥500: ↓ body weight gain in M – ≥250:↓ body weight gain in F Recovery in surviving animals Within 6 days post-dose for all symptoms (except for soiled perineal region which was noted at 12 days post-dose in 1 high-dosed animal). Reduced bodyweight gain was recorded up to 7 days post-dose in animals receiving ≥ 500 mg/kg.

Repeat dose toxicity

Four-week studies with a daily dosing regimen were performed in both rats and dogs with artesunate and pyronaridine tetraphosphate administered separately or in combination (rats only). A number of findings were reported in rats and dogs treated with pyronaridine tetraphosphate, either alone or in combination with artesunate. Most were related to accumulation of pyronaridine in many organs / tissues, which is in line with its pharmacokinetic properties. In view of these results, the applicant performed 4-week studies with consecutive dosing for 3 days per week in order to avoid / limit clinically irrelevant tissue overload with pyronaridine, and more closely represent the human situation. These 4-week, 4-cycle studies were conducted in rats and dogs with the combination (3:1 ratio). Dose levels of 0:0, 60:20, 150:50, 360:120 mg/kg/dose were used in rats, and of 0:0, 9:3, 24:8, 60:20 mg/kg/dose were used in dogs. Accumulation of pyronaridine still occurred in many organs/tissues seen macroscopically as yellow discolouration of organs/tissues, urine and sometimes skin, and microscopically as accumulation of basophilic material often associated with inflammatory changes in multiple organs. To provide toxicology data with direct relevance to the clinical dosing regimen, and investigate the longevity and reversibility of the effects attributed to pyronaridine, additional single-cycle toxicity studies were conducted. They consisted in the oral administration of pyronaridine tetraphosphate: artesunate to rats (0:0, 150:50, 360:120 mg/kg/day) and male dogs (0:0, 60:20 mg/kg/day) for 3 days followed by a variable non-dosing phase of up to 26 weeks and 40 weeks, respectively.

Results of the 4-cycle rat study show that basophilic, vacuolated macrophages or fine basophilic granules were present in many tissues at 150:50 and 360:120 mg/kg/dose in both sexes, and at 60:20 mg/kg/dose in females. This included the liver, lungs and kidneys where there was evidence of associated inflammatory and degenerating changes. In the spleen, basophilic vacuolated macrophages were observed in all treated animals. Increased haematopoiesis may be a consequence of decreased

RBC parameters. Basophilic macrophages infiltration and histiocytic foci were observed in lymph nodes at 150:50 mg/kg/dose and above. Notable reactive hyperplasia seen particularly in the submandibular node at 150/50 mg/kg/dose, and a number of females at 60/20 mg/kg/dose, indicated an immunological response. In the 4-cycle dog study, basophilic granules or vacuoles were noted in numerous organs in all treated groups. Inflammatory and degenerate changes were evident in the liver in all treated groups. Inflammatory change was present in the lungs in all treated groups.

With respect to the liver, in which inflammation was most severe, significant increases in AST levels were observed in male rats dosed at 150:50 and 360:120 mg/kg/dose at the end of dosing period, and this worsened during the recovery period, with statistical significance reached in females. In male rats, significant increase in ALT levels was reported in the group treated at 150:50 mg/kg/dose, and at the end of recovery. Overall, ALT and AST levels in treated rats were up to 2.8- and 3.6-fold, respectively, that of controls. Such effects on transaminase levels were not reported in dogs based on mean group values. Similarly, no effect on ALP (rats and dogs) and LDH (dogs) levels were observed. Findings reported at histopathological examination are consistent with the consequences of accumulation of pyronaridine in the liver. Importantly, findings such as hepatic necrosis or decreased protein synthesis (e.g. fibrinogen) were not reported – except for liver necrosis reported in male rats included in the fertility study dosed at 60 mg/kg daily from 4 weeks pre-coitum up to the end of the mating period.

In the 1-cycle studies, there were also inflammatory changes in the liver in both rats and dogs, which were no more observed by Day 71 and Day 85, respectively. These changes were associated initially with the presence of a blue/black pigment in Kuppfer cells, which was then degraded to a brown pigment. This brown pigment was still present of the livers of animals at final sacrifice, although at decreased extent.

An uncommon finding was reported as perivasculitis in brains of dogs, with dose-related increase in both incidence and severity, in the 4-week studies with daily and cyclic dosing, as well as in the 1-cycle study. It is agreed with the applicant that these changes are unrelated to those reported with artemisinins and of a different nature than the brain findings noted in rats. However, perivasculitis in the brain was seen in a reproducible manner in dogs treated with pyronaridine tetraphosphate and results from the 1-cycle dog study show that it could be observed for up to 28 weeks post-treatment. In spite of the lack of such a finding at the two later time-points (36- and 40-week post-treatment), the applicant acknowledges that the data does not support the full reversibility of the lesion (due notably to the small number of animals). The pathophysiology of the lesion is unknown but contrasts with the human CNS-specific Vasculitis (CNSV) and with reported cases of canine cerebral vasculitis notably because it was not associated with neurological clinical signs. Since pyronaridine tetraphosphate-treated dogs did not experience such symptoms, a direct comparison cannot be made at this point. But importantly, the histopathological brain lesion was shown to be at least partially reversible in these dogs. Nevertheless, the mechanism underlying brain perivasculitis in dogs is not identified, and the clinical data obtained with Pyramax, although not suggesting neurological toxicity, should be interpreted with caution due to the underlying disease (malaria) and difficulty to diagnose CNSV in humans. Therefore, since human relevance is unknown, SmPC section 5.3 has been amended to reflect the brain findings noted in dogs.

The basophilic granules were also found in the eyes of rats (not of dogs), which persisted after the recovery period. However, ophthalmologic and histopathologic examinations revealed no damage to the eyes. In the single-cycle rat study, drug-related pigmented macrophages were reported at low incidence and minimal severity in the uveal tract of treated animals only. Recovery was reached at the low-dose level (AUC-based rat-to-human exposure ratio reaching approximately 1.2 to 1.4), but not at the high dose level. Nevertheless, this finding was not associated with any local inflammatory finding and did not worsen over time. SmPC 5.3 has been amended to reflect these data.

Genotoxicity

The genotoxic potentials of pyronaridine tetraphosphate and artesunate, either as single agents or in combination (3:1 ratio) were evaluated in a range of genotoxicity assays.

For pyronaridine tetraphosphate, positive results were obtained in most *in vitro* assays with and without an exogenous metabolic activation system. A mutagenic effect was reported on Salmonella strain TA1537, chromosome exchanges and polyploidy were observed in the chromosomal aberration test on CHL cells, whilst increased mutation frequency predominantly due to small colony formation was reported in the mouse lymphoma assay. The only *in vitro* negative finding was obtained in a COMET assay on V79 cells. Two mouse bone marrow micronucleus tests were negative; the outcome of three previous mouse bone marrow micronucleus tests could not be evaluated due to the apparent presence of lots of artefacts and the incapacity to distinguish these from true micronuclei due to the use of Giemsa stains. Overall, it is concluded that pyronaridine does not induce micronuclei in bone marrow of mice. And last, an *in vivo* UDS test on rat hepatocytes gave negative results.

The applicant showed that pyronaridine is a topoisomerase II inhibitor which may act as both a catalytic inhibitor and a topoisomerase II poison dependent upon exposure concentration. The positive results obtained in various *in vitro* tests are likely related to this activity. Since topoisomerase II inhibition is a mechanism of genotoxicity with threshold dose-response relationship, it could be possible to calculate safety factor for PND-induced genotoxicity. The applicant performed an *in vivo* rat liver COMET assay. In the conditions of this assay, pyronaridine did not induce significant DNA damage in the liver of rats treated orally with up to 2000 mg/kg/day of pyronaridine tetraphosphate. At this high dose level, the concentration of pyronaridine in rat liver reached 3680 µg/g. Thus, it is concluded that there was no DNA damage in rats at pyronaridine concentrations in the liver approximately 45-fold higher than the estimated concentration of PND in the liver of human patients (estimation based on the Cmax blood/liver ratio in the rat distribution study and Cmax in the blood of patients). This safety factor is considered sufficient, in view also of the negative results obtained in mouse bone marrow micronucleus tests which are sensitive to the detection of topoisomerase II inhibitors.

Artesunate was shown to be devoid of genotoxic potential in an ICH-compliant battery of tests.

Carcinogenicity

Carcinogenic studies were not conducted due to the short clinical treatment course (limited to 3 days).

Reproduction Toxicity

Reproduction toxicity studies were performed with pyronaridine tetraphosphate and artesunate administered as single agents on a daily basis.

No effect on fertility and early embryonic development was reported in rats treated with pyronaridine tetraphosphate at up to 180 mg/kg/day. The same conclusion is drawn for artesunate at doses up to 90 mg/kg/day (males) or 16 mg/kg/day (females), in spite of an increase in the incidence of morphological sperm abnormalities observed in treated males but without dose-relationship and significant at the mid-dose level only (30 mg/kg/day). The maximum exposure to pyronaridine was approximately 2-3 times the human exposure based on AUC. Exposure to artesunate was below the human exposure.

After administration of pyronaridine, early resorptions and abortions were observed in rabbits (at 120 mg/kg/day) and decreased fœtal body weight in rats (at 420 mg/kg/day) and rabbits (at 120 mg/kg/day). In both species, effects occurred at maternally toxic doses. No teratogenicity was observed. There was no safety margin for the observed effects: as exposure ratios calculated at the

embryo-foetal NOAEL based on pyronaridine blood concentrations amounted to 2 in rats and ranged from 0.2 to 1.5 in rabbits. Artesunate was shown to be embryolethal in rats and rabbits and foetotoxic in rats where it increased the incidence of skeletal and visceral variation. Findings in rats were reported at non maternotoxic dose levels. Published data show that embryolethality results from artesunate-related depletion of embryonic erythrobasts, which leads to severe anaemia. The systemic exposure (plasma levels) in both species at the NOAEL for embryo-foetal development was well below that reached in humans. Published studies also showed that artesunate is embryo-lethal in Cynomolgus monkeys.

In the peri-post-natal toxicity study conducted with pyronaridine tetraphosphate, some effects were reported in F1 offspring at the high dose level of 150 mg/kg/day which induced maternal toxicity. At the intermediate dose levels, the weight of testes was decreased but no impact on the fertility of these animals could be observed. The exposure at 150 mg/kg was only slightly above the human therapeutic exposure. In the study conducted with artesunate, there was an increased amount of total litter losses as well as a decreased postnatal survival of F1 pups up to day 4 at 8 mg/kg/day, at exposures which were below the human exposure. There was no maternal toxicity that could explain the effects. There was no effect on F2 pups.

Pyramax is currently indicated for children who weigh more than 20 kg. Juvenile toxicity studies are currently ongoing to support a future submission for children weighing less than 20 kg.

Other toxicity studies

Compounds that accumulate in skin and eye can sometimes be associated with a risk of phototoxicity. Regarding the evaluation of the phototoxic potential of pyronaridine tetraphosphate, the applicant relies on a study published in the literature (Shao et al., 1986), thus providing limited non-clinical data evidence of a lack of phototoxic potential in mice. Phototoxicity testing is not required for artesunate in view of its absorption spectrum.

Regarding the impurities in the artesunate drug substance, studies were submitted for qualification of impurity C. Although the 14-day rat study is acceptable to qualify the impurity regarding the general toxicity aspects, concerns were raised regarding the low concentration levels used in the Ames test and the MLA-TK assay that were initially submitted. These studies were repeated using higher concentration levels of impurity C. Regarding the mouse lymphoma assay, it was recommended to repeat experiment 2 in the absence and presence of S9. Final data confirm that impurity C is at most weakly genotoxic. Considering the therapeutic indication, the short treatment period (3 days), and also the fact that pyronaridine itself is also genotoxic to some extent (as well as other anti-malaria agents), impurity C is not expected to cause a relevant extra risk.

2.3.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment is not required for a request for Scientific Opinion under Article 58 of Regulation (EC) No 726/2004.

2.3.6. Discussion on non-clinical aspects

Significant experience with artesunate is available in humans since its use is recommended by the WHO for the treatment of various forms of malaria. Therefore, the assessment was primarily focused on the nonclinical profile of pyronaridine tetraphosphate. In line with the recommendations set up for

artemisinin-based combination therapies, this compound is characterized by a long elimination half-life. Consequently, most of the findings reported in the toxicity studies conducted in rats and dogs were related to accumulation of pyronaridine in many organs and tissues and no safety margin could be determined.

Regarding genotoxicity, it is considered that the positive results obtained in various *in vitro* tests are likely related to the inhibition of topoisomerase II by pyronaridine. Since topoisomerase II inhibition is a mechanism of genotoxicity with threshold dose-response relationship, it could be possible to calculate a safety factor for pyronaridine-induced genotoxicity. In a rat liver COMET assay, there was no DNA damage in rat livers at pyronaridine concentrations approximately 45-fold higher than the estimated concentration of pyronaridine in the liver of human patients. This safety factor is considered sufficient, in view also of the negative results obtained in mouse bone marrow micronucleus tests which are sensitive to the detection of topoisomerase II inhibitors.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, all issues raised are considered resolved.

The main preclinical findings are summarised in SmPC, section 5.3.

In view of the identified hepatotoxic potential of pyronaridine (see also further discussion under "clinical aspects"), a mechanistic trial (to study impact on mitochondrial function, potential interaction with redox sensitive proteins notably as compared to amodiaquine) is recommended.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The study reports contain statements 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. As such, 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.

A routine GCP inspection has been performed at the sponsor site (Korea) and in two investigational sites (Mae Sot in Thailand, Siaya District in Kenya) in which patients were recruited for studies SP-C-004-06 / SP-C-006-06 and SP-C-005-06 / SP-C-007-07 respectively.

According to the integrated inspection report, the inspected sites are reliable. The final conclusion was that there were no findings that would preclude acceptance of the safety and efficacy data provided from sponsored studies.

The inspectors provided following recommendations to the CHMP:

- to evaluate the decision tree of parasitological efficacy and the adjudication retained for patients with discrepancies between local parasitaemia values, central QC and PCR.

- to evaluate the rationale of the definition of the EE population for parasitological efficacy at Day 28 and its consequence. This also applies to the definitions of the EE population at Day 35 and Day 42.
- for PK, to request additional documentation on the reconciliation between timepoints initially planned, samples drawn at sites, samples received and assayed at the Central lab as well as the results, if deemed necessary for the evaluation.

In the Day 120 and subsequent response documents, the applicant has provided substantial explanations that addressed the Inspection Report recommendation regarding the decision tree of parasitological efficacy and the adjudication (i) as well as the rationale for the EE populations used for the presentation of the results (ii). Regarding the PK Inspection issue, the proposed request was not deemed necessary by CHMP.

Overview of submitted clinical studies

The applicant conducted one phase I **(SP-C-001-03)** study in healthy adults and two phase II dose exploration studies, one in adults **(SP-C-002-05)** and one in children **(SP-C-003-05)** with uncomplicated *Plasmodium falciparum* malaria, including partial pharmacokinetics assessments.

Two phase III studies were conducted to evaluate the efficacy and safety of the pyronaridine tetraphosphate / artesunate (PA) fixed dose tablets (180:60mg) in adults and children (≥20 kg body weight) with acute uncomplicated *Plasmodium falciparum* malaria as compared to mefloquine plus artesunate (MQ+AS) combination **(SP-C-004-06)** and to artemether/ lumefantrine (AL) combination **(SP-C-005-06)**.

In addition, one phase III study **(SP-C-007-07)** which evaluated the efficacy and safety of a paediatric PA 60:20 mg granule formulation in children younger than 12 years (weighing from 6 to 25 kg) with acute uncomplicated *P. falciparum* malaria has been submitted. Although no application has been made for the granule formulation, this study is assessed in the present application considering the additional data it provides on the paediatric population.

Two phase III study evaluated the efficacy and safety of the pyronaridine /artesunate (PA) fixed dose tablets (180:60) in patients with *Plasmodium vivax* malaria. **SP-C-006-06** included children and adults (range 7 to 60 years) and ≥20 kg body weight. Due to slow recruitment, **SP-C-008-07** was terminated prematurely by the sponsor after 30 adults had been included. The study report was contained in the 3rd applicant's response document (submitted in October 2011).

In addition, a bioequivalence study in healthy subjects between the tablets used in the clinical phase III trials and the "to be marketed" (TBM) tablets has been submitted as well **(SP-C-009-07).** A drug interaction study with ritonavir was conducted **(SP-C-10-10).**

- Tabular overview of clinical studies

Table 2A Phase I studies:

Study ID	Design	Test Product(s) / Study Posology	Study Objective	Subjs by arm entered/ compl.	Incl. criteria
SP-C-009-07	Phase I, randomized, single dose, 2 way cross-over study.	4 to-be-marketed tablets (180:60 mg) vs. 4 clinical trial reference tablets (180:60 mg)	Bioequivalence of pyronaridine artesunate to-be-marketed tablet to the clinical trial reference tablet.	42 enrolled: 40 analysed for the reference treatment. 39 analysed for the test treatment.	Healthy subjects
SP-C-001-03	Phase I, 4 part RCT, double-blind	orally administered PP and AS	Assess the safety, tolerability, PK and potential for interaction of the combination	125 planned. 108 randomised. 105 completed.	Healthy subjects
SP-C-010-10	Phase I, randomized, three day dosing drug interaction study	3 day dosing of to be marketed tablets	Drug interaction of pyronaridine artesunate with ritonavir in healthy subjects	34 subjects enrolled. 29 subjects completed	Healthy subjects

Table 2B Phase II/III studies:

Study ID	locations	Study dates	Design	Test Product(s) / Study Posology	Study Objective	Subjs by arm entered/ compl.
Plasmodium falciparum						
SP-C-002-05 (Phase II)	Thailand, Uganda, Cambodia, Indonesia, Senegal, and The Gambia	18 -07-05 / 22-04-06	Phase II, double-blind, RCT	Group A: 6 : 2 mg/kg (PP+AS) Group B: 9 : 3 mg/kg (PP+AS) Group C: 12 : 4 mg/kg (PP+AS)	Safety and efficacy in adults with acute uncomplicated *P. falciparum*	A: 160/131 B: 157/145 C: 159/146 D: 117/43
SP-C-003-05 (Phase II)	Gabon	09-06-06 / 28-12-06	Phase II, open label, sequential, dose escalation study.	Group A: 6 : 2 mg/kg (PP+AS tablets) Group B: 9 : 3 mg/kg (PP+AS tablets) Group C: 12 4 mg/kg (PP+AS tablets) Group D: 9 : 3 mg/kg (PP+AS) (Granules)	- PK (≥10 - <40 kg) - BA of PP, AS, and DHA - safety and tolerability - PD profile	A: 14/10 B: 15/8 C: 15/15 D: 15/14
SP-C-004-06 (Phase III)	Thailand, Vietnam, Cambodia, India, Ivory Coast, Burkina Faso, Tanzania	25-01-07 / 02-10-08	Phase III open-label RCT non-inferiority	PA 180:60 mg tablets MQ (250 mg) + AS (100 mg)	To compare the efficacy and safety of the fixed combination of PA (i.e., PP + AS) (180:60 mg) with those of MQ + AS in subjects with	PA: 848/723 MQ + AS: 423/357

					acute, uncomplicated *P. falciparum* malaria	
SP-C-005-06 (Phase III)	Senegal, Gambia, Ghana, Kenya, DRC, Indonesia, Philippines, Mali, Mozambique	18-01-07 / 04-04-08	Phase III RCT, double-blind, non-inferiority	PA 180:60 mg (tablets) AL 20:120 mg .	Efficacy and safety of PA vs. AL in patients with acute, uncomplicated *P. falciparum* malaria	PA: 849/751 AL: 423/347
SP-C-007-07 (Phase III)	Burkina Faso, DRC, Gabon, the Ivory Coast, Kenya, Mali, The Philippine	19 -11-07 / 25-09-08	Phase III RCT open-label non-inferiority	PA, 60:20 mg **(Granules**) AL 20:120 mg crushed	Efficacy of PA granules by showing a PCR-corrected ACPR of >90%. and Efficacy (non-inferiority) and safety of PA granules formulation to AL crushed tablets	PA: 355/274 AL: 180/142
Plasmodium vivax						
SP-C-006-06	Cambodia, India, Indonesia, and Thailand	10-03-07 / 31-03-08	Phase III RCT double-blind, Non-inferiority	PA 180:60 mg tablets or CQ 155 mg	Efficacy and safety of PA vs. CQ therapy in children and adults with acute, uncomplicated *P. vivax* malaria	PA: 228/193 CQ: 228/187
SP-C-008-07 (submitted in October 2011)	Korea (2 sites)	6-09-07/ 5-10-10 **Prematurely terminated by the sponsor due to slow recruitment**	Phase III RCT double-blind, Non-inferiority	PA 180:60 mg tablets or CQ 155 mg	Efficacy and safety of PA vs. CQ therapy in children and adults with acute, uncomplicated *P. vivax* malaria	PA: 15/15 CQ: 15/15

2.4.2. Pharmacokinetics

Analytical methods

In the course of PK development of Pyramax, whole blood was the biological matrix selected for pyronaridine investigation, whilst plasma was used for the investigation of artesunate and DHA. From the data available it is clear that the plasma PK profile of pyronaridine is not parallel to that obtained from whole blood due to uptake of the drug by Red Blood Cells (RBC). Therefore, the characterization of pyronaridine through whole blood levels appears to be fully justified. Conversely, artesunate and DHA were monitored in plasma.

LC-MS technique was used for the measurement of artesunate and DHA in plasma. This technique seems fully validated and fit for the purpose.

Alternatively, HPLC-UV and LC-MS techniques were used for the measurement of pyronaridine blood levels. According to the applicant this technique is fully validated and fit for the purpose. The validation

data are reported. In some studies, pyronaridine levels in urine were tested. This method is also sufficiently validated.

Adequate methods including widely used software for pharmacokinetic data estimation and statistical analysis were used.

Absorption

Pyronaridine is highly soluble in water, while artesunate is slightly soluble.

No attempt to elucidate the absorption mechanism of the actives of Pyramax (non-passive diffusion and identification of transporters) was made by the applicant. However, data from studies conducted in healthy volunteers indicate that the onset and the rate of absorption of artesunate are very rapid. Detectable levels were obtained within less than 0.25 h and Cmax being reached at approximately 0.5 hours after oral administration. Despite being more soluble, the absorption of pyronaridine appears to be slower but still also rapid. Plasma peak concentrations were reached within 4 hours approximately.

The absolute bioavailability of Pyramax active substances (pyronaridine and artesunate) has not been tested by the applicant. But, according to published literature, absolute bioavailability of artesunate by oral route is low (approximately 15-23), however the relative bioavailability of DHA following oral artesunate was high, with mean values of 82% and 85%. This suggests that artesunate underwent an extensive pre-systemic metabolisation.

No data regarding the absolute bioavailability of pyronaridine is available as no intravenous formulation was available.

Throughout pharmaceutical development, formulation changes were made in order to improve manufacturing efficiency and to increase potential for adjusting tablet weight. Therefore, the relative oral bioavailability of the to-be-marketed tablet and the clinical trial reference formulation was investigated in one bioequivalence study (SP-C-009-07). From this study and from pharmaceutical considerations (*in vitro* dissolution tests and formulation comparison), there is reasonable evidence that these different investigational drug products perform similarly.

The effect of food intake on the bioavailability of Pyramax active substances was tested in one study (SP-C-001-03). The food effect study did not suggest any clinically relevant effect of food on the bioavailability of either compound and therefore Pyramax can be taken with or without food.

Distribution

No estimation of the initial volume of distribution could be made for pyronaridine or artesunate as pharmacokinetics of these components was not characterized by intravenous route.

- Preclinical data indicate an extensive distribution of pyronaridine to body tissues in Rats. *In vitro* studies showed that at plasma level pyronaridine is mainly bound to plasma proteins. The unbound fraction is approximately 5-10 %. Also, it was shown that pyronaridine is up-taken by blood cells with a ratio blood cells/plasma being approximately 1.6 % in Rats. Poor information is available regarding pyronaridine distribution in humans. In the response document, the applicant indicated that a mass-balance/absolute bioavailability study would be initiated shortly. It is expected that distribution would be elucidated by the planned investigation.
- No specific investigations have been carried out by the applicant in order to characterize the distribution of artesunate and DHA in Human. From the published data there is evidence that artesunate and its active metabolite bind moderately to plasma proteins and mainly to HSA (Human Serum Albumin). No information is available regarding uptake of artesunate and DHA by

Red blood cells. Information regarding uptake (binding) of artesunate and DHA by red blood cells is lacking.

Elimination

In the initially submitted documentation, no specific investigation was performed by the applicant in order to elucidate the elimination pathways of pyronaridine and artesunate.

No reliable attempt to elucidate the metabolism pattern of pyronaridine in Humans was made. From the very limited available *in vitro* data, pyronaridine appears to be poorly metabolized by human liver microsomes. However, considering the lack of appropriate *in vivo* investigation no conclusions could be drawn. During the procedure the applicant has initiated a mass-balance/absolute bioavailability study. An interim report of this study (SP-C-012-11) has been provided by the applicant in December 2011. The mass-balance study was performed in six male healthy volunteers orally receiving the dose of 720 mg [14 C] pyronaridine tetraphosphate. Only data regarding total radioactivity in plasma and excretes are reported. Urine and faeces samples were collected over an 86-days period post dosing. It was observed that measurable levels of radioactivity were still being recovered at the last collection point (0.23% dose between 2016-2064 hours, equivalent to approximately 0.8% dose/week). The total cumulative fraction that was recovered was 71.5 % with 23.7±4.48 % and 47.8±8.94 % respectively in urine and faeces. Based on the data available at the present time, the elimination pathways of pyronaridine are still not elucidated. Though a significant extent of renal excretion appears unexpectedly identified for pyronaridine related materials, the respective contribution of renal and hepatic routes in the elimination of pyronaridine cannot be estimated for the time being as only levels of total radioactivity are reported by the applicant. The applicant states that characterisation of drug-related material in whole blood and excreta is in progress. The identification and quantification of radio-labelled drug-related material should be performed and its outcome reported.

The estimated half life of total radioactivity is much longer than that anticipated for pyronaridine. This would suggest the formation of metabolite(s) with very long half-life and high potential for accumulation. This issue should be elucidated when the data regarding identification and quantification of metabolites becomes available.

According to published data, artesunate is rapidly hydrolyzed to DHA, primarily by plasma or tissue choline esterases. Due to the rapid conversion, artesunate is often considered as pro-drug of DHA. Following oral administration of artesunate, the ratio of AUC for DHA to AUC for artesunate can be as high as 10:1. The metabolic pathways for DHA was studied in humans by analyzing metabolites in urine collected from patients who had received intravenous AS and metabolites produced by human liver microsomes. Using V79 cells expressing different human UDP-glucuronosyltransferases (UGTs), such as UGT1A1, UGT1A6, UGT1A9 and UGT2B7, it was shown that DHA is metabolized by UGT1A9 and UGT2B7, but not UGT1A1 and UGT1A6. The major metabolite identified was α-DHA-β-glucuronide. AS and DHA undergo extensive first-pass metabolism with very high extraction ratio. For drugs with high extraction ratio, clearance approaches blood flow and is therefore perfusion rate limited.

In order to better characterize, pyronaridine PKs (absorption, distribution and elimination), the applicant initiated a mass-balance study using radio-labelled pyronaridine. The study is still ongoing and the final results are not yet submitted. Therefore, pyronaridine PK characteristics remain not elucidated.

Dose proportionality and time dependencies

There is no marked shift from dose proportionality of pyronaridine, artesunate and DHA PKs after administration of single or repeated (for three days) escalated doses up to 15/5 mg/kg (PYR/AS 3:1 fixed dose combination).

Pyramax is not intended for long term use. Therefore, time dependency is not a crucial issue. However, it is noteworthy, that the obtained data evidenced no auto-induction of artesunate, as previously described in literature for other artemesinin derivatives.

Special populations

From the available data, the inter-subjects variability of systemic exposure to artesunate, DHA and pyronaridine appears to be high (approximately 50 to 100%). No reliable information regarding intra-subject variability is available.

A population-PK reanalysis of data was performed by the applicant including almost all the available data from Phase I, II and III. Formulation was tested as a categorical covariate with two levels: tablet and suspension. Although different tablet formulations and strengths were used in the Phase I and II studies, sufficient support is submitted that the bioavailability is expected to be comparable.

In addition, the inclusion of age as a categorical variable resulted in unreasonable parameter estimates, and therefore, was not included in the final model. Therefore, the developed model could not be considered relevant for the characterization of Pyramax components PKs in paediatric patients. However, the applicant intends to perform a study in paediatrics, which will investigate efficacy/safety of Pyramax and adequacy of the dosing regimen in paediatric population.

<u>The following observations are made:</u>

- Lower systemic exposure is observed in malaria patients comparatively to healthy volunteers. This lower exposure is linked to the larger volume of distribution observed in malaria patients.
- Limited data are available in subjects with **renal impairment**. Therefore, no conclusions could be made from the population-PK analysis regarding the systemic exposure to Pyramax components in patients with renal impairment. Although excretion via faeces was the main route of elimination of pyronaridine-related material in a human mass balance study, significant urinary excretion was also observed. Pyramax is, therefore, contraindicated in the case of severe renal impairment. Proper warnings were introduced in the SmPC, section 4.2. (contra-indication in severe renal impairment patients and caution for use in patients with mild to moderate impaired renal function).
- Poor data are available in subjects with **hepatic impairment**. Therefore, no conclusions could be made from the population-PK analysis regarding the systemic exposure to Pyramax components in patients with liver impairment. There is no information on dosing with patients with hepatic impairment. Data from a mass balance study with pyronaridine in healthy volunteers indicates that faeces is the main route of elimination of drug-related material. Pyramax is contraindicated in the case of hepatic impairment. A statement to this effect was introduced in SmPC, section 4.2
- Regarding AS and DHA: artesunate is a water-soluble hemisuccinate ester of DHA; esterase-catalyzed hydrolysis of the ester bond *in vivo* yields DHA as the active metabolite of artesunate. DHA is metabolized through conjugation with glucuronic acid by the UDP-glucuronosyl transferase system. Specifically, UGT1A9 and UGT2B7 appear to be the primary isoforms responsible for DHA metabolism. Protein binding of AS and DHA is moderate. Hepatic impairment is considered not to have a pronounced impact on the pharmacokinetics of AS and DHA.
- **Gender** does not influence significantly the PK behaviour of artesunate and DHA or pyronaridine.

- Limited data are available in **obese and underweight** patients. However, no dosage adjustment is deemed to be necessary in these sub-groups as dosage recommendation is based upon body weight.
- No differences in AS/DHA or pyronaridine PKs linked to **ethnicity** are evidenced.
- No appropriate PK investigation has been performed in **elderly** subjects and no reliable safety data are available in patients over 65 years and this has been reported in the SPC. Considering the lack of data, Pyramax should be used cautiously in patients over 65 years
- A **paediatric** granule formulation was used in some clinical studies. The present application doesn't pertain to any granule formulation. The applicant has planned to develop a granule formulation as it is a more suitable presentation for paediatric dosing in very young children. Based on the presently available data, the bioequivalence between the granule formulation used in the available phase III clinical trials and the tablets formulation is however not established and thus precludes any extrapolation from the granule studies to the tablet use. The applicant commits to perform a new bioequivalence study and also to initiate a clinical study in paediatric population using a granule presentation. Until these data become available, the PK data do not support the indication of Pyramax in children less than 20 kg.

Pharmacokinetic interaction studies

There is no marked potential for interaction between the active components of Pyramax (pyronaridine and artesunate) (SP-C-001-03).

A clinical drug-drug interaction study was conducted with Pyramax and the protease inhibitor ritonavir (SP-C-010-10).

In vitro data indicate that Pyramax could interact with drugs metabolised by CYP2D6. The inhibitory effect of pyronaridine on CYP2D6 showed an IC_{50} of 1.1 µM (569 ng/mL). Based on the suggested dosing regimen of Pyramax in the claimed indication, the pyronaridine concentrations will exceed 569 ng/mL after repeated administration, indicating that a clinical relevant interaction is likely. An *in vivo* drug-drug interaction study is planned using metoprolol as CYP2D6 substrate in order to assess the magnitude of the interaction and to provide adequate recommendations in the SmPC. Meanwhile, a warning is included with drugs metabolised via CYP2D6.

In addition, *in vitro* data show that Pyramax, (i.e. the combination of pyronaridine and artesunate) is an inhibitor of P-gp. The clinical relevance of such an inhibition could also be further explored in an *in vivo* drug-drug interaction study with Pyramax and a probe substrate of this transporter, e.g. digoxine or dabigatran.

An additional study investigated the inhibition potential of Pyramax for CYP2B6 and CYP2C8. There was no appreciable inhibition of CYP2B6 or CYP2C8 with artesunate, DHA or pyronaridine at concentrations up to 50, 25 and 25 µM, respectively. In addition, artesunate, DHA and pyronaridine showed no evidence of time-dependent inhibition of CYP2B6 or CYP2C8.

Another additional study investigated the activity of DHA to inhibit UGT-mediated metabolism, the affinity (Km) of DHA for UGT1A9 and UGT2B7, and the potential for UGT-mediated DDI between DHA and AZT. DHA was shown to have no appreciable inhibitory effect on UGT1A1, UGT1A3, UGT1A6 or UGT1A9 at the maximum tested concentration of 25 µM. DHA had a weak inhibitory effect on UGT2B7, with 48% inhibition at 25 µM indicating the IC50 should lie close to this concentration. The Km of DHA for UGT1A9 and UGT2B7 was estimated to be >100 µM and approximately 30 µM, respectively. AZT had no significant effect on DHA glucuronide formation via UGT2B7, however, at 25 and 50 µM, DHA reduced the formation of AZT glucuronide by 48 and 63% respectively.

Overall, there is no evidence to suggest that the metabolism of DHA to DHA glucuronide is likely to be subject to drug-drug interactions, but DHA could inhibit UGT2B7-mediated metabolism above 25 μM. However, simulations demonstrated that, even when more than 60% of a substrate's metabolism is via a single UGT isoform, a clinically significant drug-drug interaction (defined as greater than 2-fold increase in AUC in the presence of an inhibitor) required the concentration of inhibitor to be 10-fold higher than the inhibitory constant (Ki). Assuming simple competitive kinetics, then the IC50 of DHA for UGT2B7 being approximately 25 μM, equates to a Ki of 12.5 μM, thus suggesting that concentrations of DHA would need to reach 125 μM before a clinically significant DDI was likely. The Cmax for DHA, on the third day of the 3 day treatment course, during a Phase I study with the highest therapeutic dose level of 5 mg/kg artesunate, was 1221 ng/mL (4.3 μM). Human liver concentrations of DHA are unknown, but the volume of distribution of DHA at steady state is reported to be approximately 2 L/kg, suggesting that liver concentrations will not be much higher than plasma concentrations. Therefore, clinically significant UGT-mediated drug-drug interactions seem unlikely during therapeutic use of Pyramax.

This weak inhibitory potential shown for UGT2B7 (IC_{50} = ~25 μM), along with the DHA C_{max} value in healthy subjects (4.3 μM, even if 2 to 4 fold higher in malaria patients) gives poor likelihood to achieve DHA concentrations impacting UGT2B7 activity in a relevant way.

Multiple dose administration of AS did not alter the pharmacokinetics of artemisinin; however, artemisinin co-administration with artesunate in ten healthy adults was associated with a more than two-fold increase in DHA AUC, a finding which led the authors to speculate that artemisinin may act as a UGT inhibitor.

Overall, the data suggest that UGT-mediated DHA-glucuronidation is not influenced by DHA. Moreover, drugs with impaired metabolism through UGT2B7 inhibition or induction are very few, and as far as it could found, none of them has been involved in such a PK mechanism so far. Experience on the existence of any clinical consequences of UGT2B7 inducers or inhibitors could neither be found.

2.4.3. Pharmacodynamics

Mechanism of action

Pyronaridine

No specific *in vitro* study has been provided by the applicant.

Pyronaridine is a hydroxyanilino-benzonaphthyridine acridine derivative which also includes amodiaquine-like side chain. Initial published experiments indicated that pyronaridine interfered with the digestive system of trophozoites in erythrocytic *P. falciparum* and P. *berghei* cultured *in vitro* [Wu et al. 1988] and of late trophozoites and schizonts in primates infected with *P. falciparum* [Kawai et al. 1996]. However, subsequent published *in vitro* studies reported a different mechanism. During the blood stage of the parasite, more than 70% of the haemoglobin within an infected erythrocyte is digested to haem which is toxic for the parasite and therefore neutralized by the parasite into haemozoin, an insoluble polymer based upon haematin. Pyronaridine (0.125 mM) inhibits β-haematin production and forms complexes with haematin to enhance haematin-induced human blood cell lysis [Dorn et al. 1998; Auparakkitanon et al. 2006] and to inhibit glutathione-dependent degradation of haematin [Famin et al. 1999; Auparakkitanon et al. 2006].

Pyronaridine has been used in China for over 30 years mainly as single agent; initial clinical trials were conducted in China. Its safety and efficacy by oral and parenteral routes against both *P. falciparum* and

P. vivax has been described in literature [Fu, 1991; Chen, 1992; Chang, 1992]. The drug has also been described to be effective in treating malaria patients in some other regions [Ringwald-Africa, 1996; Looareesuwan-Bangkok 1996].

Artesunate

No specific *in vitro* study has been conducted by the applicant.

Artesunate is an artemisinin derivative. Artemisinin derivatives have been shown to be selectively toxic to malaria parasites. Based on available literature, artemisinin derivatives have been reported as having a two step mode of action. In the first step artemisinin compounds are activated by haem (released during the blood stage of the parasite when haemoglobin is digested) or Fe^{2+} to produce free radicals and alkylating intermediates [Meshnick et al. 1993; Kamchonwongpaissan and Meshnick, 1996]. This is followed by a second step in which these reactive species react with and damage specific membrane associated proteins [Meshnick et al. 1991, Meshnick 1994]. The role of oxygen radicals is supported by the hypothesis that the *in vitro* antimalarial activities of artemisinin and artesunate are enhanced by either high oxygen tension or other free radical generating compounds such as doxorubicin or miconazole, but are blocked by antioxidants such as catalase and dithiothreitol [Krungkrai and Yuthavong 1987]. However, haem-dependent activation of artemisinins ignores two major issues. First, artemisinins localize in the tubovesicular membrane network in red blood cells which transport the drug into the parasite and parasite membranes rather than in the food vacuole membranes (where there is an increased chance for availability of labile iron) [Ellis et al. 1985]. Second, artemisinins kill the early ring stages of *P. falciparum*, which do not yet metabolize haemoglobin and which therefore lack haemozoin [Eckstein-Ludwig et al. 2003]. Indeed, in experiments using the protease inhibitor (Ro 40-4388), that blocks haemoglobin degradation preventing the release of haem *in situ*, the activity of chloroquine, whose anti-malarial action is also dependent on its binding to haem, was attenuated whilst, no antagonism or synergism was observed between the protease inhibitor and artemisinin activity, thus providing evidence for haem- or Fe2+-independent activation of artemisinin [Eckstein-Ludwig et al. 2003].
The artemisinin membrane–induced effects were thought to underlie other observed effects of artemisinin derivatives such as haemolysis [Gu et al. 1986], decreased erythrocyte deformability [Scott et al. 1989] and premature lysis of infected erythrocytes [Gu and Inselberg 1989]. However, some of these actions only occur at high drug concentrations (>100 µM) suggesting that they may be non-specific and hence, may not explain artemisinin-induced parasite death.
Inhibition of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) of the malarial parasite might be an alternative mechanism of action for artemisinins, since inhibition of PfATP6 expression, the only SERCA sequence in the genome of *P. falciparum* and which is present outside the food vacuole, strongly correlated with the ability of artemisinin to kill parasites *in vitro* [Eckstein-Ludwig et al. 2003]. Overall, the pivotal event leading to parasite death remains to be elucidated.

Mechanism and development of resistance

No specific investigations have been performed by the applicant on mechanism of development of resistance. All data are from published references.

The mechanism by which resistance to pyronaridine develops is unknown. The activity of pyronaridine against chloroquine-sensitive and -resistant field isolates has been investigated in several studies. Most of the publications presented in the dossier are over 10 years old. *In vitro* cross resistance of pyronaridine with chloroquine appears to be incomplete and inconsistent. In summary, the relationship between pyronaridine and chloroquine susceptibility in *P. falciparum* appears to be more complex than simple cross resistance and may vary regionally suggesting differences between chloroquine and pyronaridine resistance and more than one resistance mechanism may operate. In a recent published

study that evaluated the *in vitro* cross-resistance of pyronaridine with other quinoline drugs, artesunate and other commonly used antimalarials in 23 strains of *P. falciparum*, the ACT components pyronaridine and artesunate were found to be active against chloroquine and pyrimethamine-resistant strains as well as against parasites with reduced susceptibility to quinine, monodesethylamodiaquine or mefloquine (Pradines et al., 2010). The absence of cross resistance between pyronaridine and quinolines and the fact that IC_{50} values for pyronaridine were found to be unrelated to mutations in transport protein genes involved in quinoline anti-malarial drug resistance is in favour of the efficacy of pyronaridine and artesunate for areas in which parasites are resistant to chloroquine or other quinoline drugs (Ramharter et al., 2008, Kurth et al., 2009). Still, a moderate *in vitro* correlation on *P. falciparum* was observed between pyronaridine and amodiaquine and piperaquine in a recent publication (Price RN, AAC 2010).

Investigations into the stability of pyronaridine resistance have reported mixed findings. Trials were performed only on rodent plasmodium strains (*P. berghei, P. yoelii*). Resistance to pyronaridine was established after a high number of passages in rodents, suggesting that resistance would be improbable. Still, as they are experimental data from animal trials and strains, any extrapolations to *Plasmodium falciparum* and to human population remain uncertain.

To date, resistance to artemisinin-type compounds has not been widely reported. Resistance of *P. falciparum* to artemisinin has been induced *in vitro* and was stable for over 6 months in the absence of drug pressure. However, patterns of cross resistance varied dependent on the clone of *P. falciparum* used (Trigg, 1989). Moreover, multiple targets for the mechanism of action have supported the lack of evidence for artemisinin resistance, in that, mutations that might reduce affinity to artemisinin would need to develop in all the targets before resistance could develop (Krishna et al., 2006). A greater understanding of both the mode of action as well as the genetic basis for altered parasite susceptibility to the artemisinins is required to elucidate potential resistance mechanisms (Ding et al., 2011). *In vitro*, resistance to artemisinin has been reported in isolates from French Guiana (Jambou et al., 2005) and genetically stable resistance to artemisinins has been reported in a *P. chabaudi* model in which resistance was maintained even after mosquito passage (Afonso et al., 2006). Others have reported that resistance was labile and difficult to induce experimentally, in that, low levels of resistance were achieved after sustained drug pressure, but not retained once drug pressure was removed (Peters & Robinson 1999). In addition, a link between between reduced *in vitro* artemisinin susceptibility and loss of clinical efficacy following artesunate monotherapy has been reported (Menard et al., 2005). At present, the threshold for resistance of *P. falciparum* to artesunate remains indeterminate however, a delayed parasite clearance-time phenotype, in patients, has recently been described in Western Cambodia (Noedl et al., 2008; Dondorp et al 2009).

The partnering of antimalarials in artemisinin-containing combination (ACT) drugs as first proposed by White & Olliaro 1998, was in part to protect the artemisinin component from the risk of development of resistance. Following administration, artesunate is converted to its active metabolite dihydroartemisinin (DHA), to rapidly eliminate parasites, after which, the drug is promptly cleared due to its short systemic half life (0.54 h). In this way, the ideal duration of partner half-life is still the cause of speculation in the malaria community. An excessively long half-life is seen to be a benefit by some experts in that it may potentially provide some protection against recrudescence or reinfection. Counter-arguments are presented that particularly long half lives may provide an environment for resistance to the single agent to be generated through drug pressure on the Plasmodium isolates. This is provided as the reason for the emergence of resistance to mefloquine and chloroquine in South East Asia.

Pyronaridine has a longer half life than artesunate and DHA (11-16 days i.e. close to chloroquine half life, in the lower limit range as compared to mefloquine [14-21 days], and longer than lumefantrine), and hence, provides a more sustained schizonticidal effect after artesunate. The clinical aim of a fixed-

dose combination with of pyronaridine and artesunate is to evoke a rapid reduction in parasitaemia, over 2 asexual cycles, using a three day dosing regime, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

2.4.4. Discussion on clinical pharmacology

The fixed-dose combination of pyronaridine tetraphosphate and artesunate in the treatment of uncomplicated acute *Plasmodium falciparum* and *Plasmodium vivax* malaria aims to provide a rapid reduction in parasitaemia with a 3-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

No specific investigations have been performed by the applicant on mechanism of action and the mechanism of development of resistance. All data are from published references.

The applicant studied patient pharmacodynamic outcomes in the form of parasite clearance in a range of phase II and phase III studies (see further).

To date, the pharmacokinetics of Pyramax has been insufficiently elucidated. In order to better characterize, pyronaridine PKs (absorption, distribution and elimination), the applicant initiated a mass-balance study using radio-labelled pyronaridine. The study is still ongoing and the final results are not yet submitted.

Data is currently missing from certain populations, in particular the paediatric population. Bioequivalence between the granule formulation used in the available phase III clinical trials and the tablets formulation is however not established and thus precludes any extrapolation from the granule studies to the tablet use. The applicant plans to perform a new bioequivalence study and also to initiate a clinical study in paediatric population using a granule presentation. Until these data become available, the PK data do not support the indication of Pyramax in children less than 20 kg.

The effect of concomitant administration of Pyramax and known CYP2D6 substrate has not yet been studied. An *in vivo* drug-drug interaction study is planned using metoprolol as CYP2D6 substrate in order to assess the magnitude of the interaction and to provide adequate recommendations in the SmPC. Routine pharmacovigilance measures are proposed for P-gp interactions (which are likely to be primarily for the concomitant use of digoxin).

2.4.5. Conclusions on clinical pharmacology

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

Study SP-C-012-11: Mass balance study in human with [14C] pyronaridine is ongoing. Interim report has been provided in December 2011 but characterisation of drug material is in progress. Final study report is expected.

Study SP-C-014-11: Phase I study: open-label, drug interaction study of Pyramax (pyronaridine:artesunate) and metoprolol (as substrate of CYP2D6) in healthy volunteers and Pyramax re-dosing study following 60 or 90 days wash out, in healthy volunteers. Total of 44 healthy subjects planned. Completion of the study is planned by May 2012. A warning is presently required in the SmPC with respect to CYP2D6.

Study SP-C-016-11: to investigate potential interactions between Pyramax and primaquine is also planned with retreatment of Pyramax as part of the design, also involving an 8 week washout period.

The above measures are noted in the RMP.

In view of future development of Pyramax, the CHMP recommends the following:

Study SP-C-015-11: absolute bioavailability study

Study SP-C-017-11: comparative bioavailability study of to-be-marketed tablets and granules and effect on milk co-administration on granule bioavailability (no time line provided).

2.5. Clinical efficacy

All clinical studies were conducted in endemic areas in both sub-Saharan Africa and Asia, but none included Central or South American countries.

2.5.1. Dose response studies

Two phase II dose-response studies, one in adults (SP-C-002-05) and one in children (study SP-C-003-05), were conducted in patients with uncomplicated *Plasmodium falciparum* malaria.

Study SP-C-002-05

This was a Phase II, double-blind, multi-centre, randomised, parallel-group, dose-finding study of orally administered pyronaridine tetraphosphate–artesunate in the ratio 3:1 (weight mg/weight mg), for the treatment of subjects with acute, symptomatic, uncomplicated *P. falciparum* malaria. The study started on 18 July 2005 (first subject enrolled) and was completed on 22 April 2006 (last subject completed study).

The study was conducted at 8 centres in South East Asia and Africa: Bangkok, Tak, Ratchabur (Thailand), Mbarara (Uganda), Phnom Penh (Cambodia), North-Sulawesi (Indonesia), Dakar (Senegal), and Banjul (The Gambia).

The primary objective of this study was to determine the clinically effective dose of orally administered PA (3:1 weight mg/weight mg) ratio, in the treatment of subjects with acute, symptomatic, uncomplicated *P. falciparum* malaria.

A total of 477 subjects were randomised in a 1:1:1 ratio in one of the 3 treatment groups.

One subject was not treated, but all others were included in the ITT/safety population.

Group	Tablet strength	PP dose	AS dose
Group A	PA (48 mg + 16 mg)	6 mg/kg	2 mg/kg
Group B	PA (72 mg + 24 mg)	9 mg/kg	3 mg/kg
Group C	PA (96 mg + 32 mg)	12 mg/kg	4 mg/kg

The dose ranges covered by this regimen were:

- Group A : 5.6:1.9 mg/kg/dose to 6.9:2.3 mg/kg/dose
- Group B: 8.4:2.8 mg/kg to 10.3:3.4 mg/kg
- Group C : 11.2:3.7 mg/kg to 13.7:4.6 mg/kg

Mean age was 27.8 years and ranged between 15 and 60 years

- **Definition of analysed populations and statistical methods**

– The intent-to-treat (ITT) and safety populations included all subjects who were randomised and received any study medication, regardless of the amount.

– The EE (Efficacy Evaluable population) population included subjects who met the following pre-defined criteria:

  - Completed a full course of study medication and had known efficacy end points.
  - No missed dose due to vomiting, as recorded on the 'study medication administration page' of the subject's CRF, except at Day 0, where a subject may have vomited the first drug administration and had a repeat full dose. In these cases, the repeated dose should not have been vomited.
  - No concomitant medication (except acetaminophen) that could have interfered with the treatment outcome, up to Day 28.
  - No concomitant disease that could have interfered with clear classification of the treatment outcome.
  - No major protocol violation with respect to entry eligibility criteria.

Analysis of the primary efficacy end point (proportion of subjects with PCR-corrected ACPR on Day 28) was performed on the EE population (Efficacy Evaluable population).

The null hypothesis was that the PCR-corrected ACPR at Day 28 was ≤95%, and the alternative hypothesis was that the PCR-corrected ACPR at Day 28 was >95%. The null hypothesis was to be rejected if the p-value associated with the one-sided exact test using the binomial probability function was ≤0.05.

In addition, the mITT population included all ITT/safety subjects except the subjects from the Phob Phra site in Thaïland (see below) and the subject who did not receive any study medication. The associated two-sided 90% confidence interval (CI) of the proportion was presented. If the null hypothesis was not rejected in any of 3 dose groups individually, the data from the group with the highest number of failures were to be excluded and the data from the other 2 dose groups were to be pooled together.

- **Results**

The primary efficacy analysis (ACPR defined as the proportion of subjects with PCR-corrected adequate clinical and parasitological rate) was performed on a predefined Efficacy Evaluable (EE) population at Day 28 but patients were to be followed to Day 42; 35% of subjects in the ITT/safety population were major protocol violators and were excluded from the EE population analysis. The majority of these subjects (138 of 142) were from the Phob Phra site in Thailand. After the data were unblinded, all of the Phob Phra subjects had unreadable slides (QC review); therefore, *P. falciparum* malaria could not be confirmed by blood smear. The modified intent to treat population (mITT) excluded those 138 patients from Phob Phra site.

PCR-corrected ACPR was found 99% at Day 28, statistically significantly greater than 95% cure rate in the EE population in the 9+3 mg/kg and 12+4 mg/kg dose groups (p=0.033 and p=0.034, respectively). The rate of cure in the 6+2 mg/kg dose group was only slightly lower than in the higher dose groups (95% vs. 99%). The same cure rates were reported in the mITT population (excluding Phob Phra population).

At Day 42, the PCR-corrected ACPR rates were 93%, 97%, 97% across 3 dose groups 6+2 mg/kg, 9+3 mg/kg, 12+4 mg/kg, respectively, in the EE population (results were: 92.9%, 97.1%, 97% in the mITT population), but was not demonstrated to be statistically significantly greater than 95%.

Apparently, there was 4 new infections and 13 recrudescences (treatment failures) i.e. n=7, n=3, n=3 across dose groups respectively, through Day 42. In response provided during assessment of the application (Day 120 assessment response), the applicant has provided some clarifications on patients who discontinued. A total of 7 patients in the 6+2 mg/kg treatment group, 2 patients in the 9+3 mg/kg treatment group, and 2 patients in the 12+4 mg/kg treatment group discontinued due to insufficient therapeutic effect. These patients had parasite reappearance during the study and were classified as either a Late Clinical Failure or Late Parasitological Failure accordingly. One patient discontinued due to vomiting after dosing (Patient G341); however the parasite sensitivity analysis was not performed for this patient.

No statistical difference among the dose groups where observed on the other variables, although a tendency to longer parasite clearance time (median: 32 hours versus 24 hours) and fever clearance time which lagged slightly behind parasite clearance, were in the lowest dose (6+2 group).

The proportion of subjects with gametocytes tended to rise during the first week and then it decreased: at Day 35, 1 subject (12+4 mg/kg dose group) had gametocytes. At the end of the study (Day 42), 3 patients had gametocytes (2 patients in the 6+2 mg/kg group and one in the 12+4 mg/kg group). The gametocytes time clearance and carriage cannot be properly assessed in this study as the collection of the gametocytes was not clearly anticipated in the CRF from this study.

In this study (28-day sampling period), conducted in adults with malaria, pyronaridine had a $T_{½,}$ of approximately 10.4 to 15.1 days.

There was little difference in efficacy among the 3 dose groups. However, the response to treatment appeared to be slowest in the 6+2 mg/kg dose group (parasite clearance time). Hence, the applicant considered the 9+3 mg/kg and 12+4 mg/kg doses were preferable than the 6+2 mg/kg dose for the clinical phase III studies.

Study SP-C-003-05

This was a Phase II, open-label, single centre, sequential-group, dose-escalation, single-centre study. The study report states that the first patient was enrolled on 09 June 2006 and last patient completed on 26 December 2006. The database was locked on 05 March 2007. The study was conducted at a single study centre in Gabon.

The primary objectives of this open label study were to study pharmacokinetics, bioavailability comparison of tablets vs. granules formulations, and safety/tolerability of pyronaridine tetraphosphate -artesunate in the treatment of paediatric subjects with acute, symptomatic, uncomplicated *P. falciparum* malaria.

A total of 60 black children aged from 2 to 14 years (mean age 5 years) and weighing 10.0 to 36.4 kg were successively enrolled (15 patients in each group) in this dose-rising study of 3 doses of PA: group A: 6+2 mg/kg (using 48 mg:16 mg tablets), group B (tablets) and D (granules) : 9+3 mg/kg (using 72 mg:24 mg tablets and 60 mg:20 mg granules), and group C: 12+4 mg/kg (using 96 mg + 32 mg tablets). Basically, the corresponding actual dose ranges covered in each group were (PP:AS): group A: from 4.2:1.4 mg/kg to 7.2:2.4 mg/kg ; group B: from 7.2:2.4 mg/kg to 11.6:3.9 mg/kg ; group C: from 10.1:3.4 mg/kg to 16.3:5.4 mg/kg ; group D: from 9.1:3.0 mg/kg to 13.0:4.3 mg/kg .

All subjects (except 2 patients who were discontinued due to vomiting) received 3 doses of study drug.

12 (20%) were withdrawn prematurely. The main reason for premature discontinuation was due to adverse events (AEs) (9 [15%] subjects; 2 due to vomiting, 6 due to re-appearance of parasitaemia, and 1 due to a *P. ovale* infection). In total, 46 subjects (78% of the 59 treated subjects) completed the study to Day 42.

The PCR-corrected ACPR on Day 28 was 100% in all 4 treatment groups (per protocol analysis) with lower 95% exact Pearson-Clopper confidence limits ranging between 71.5% in the 6+2 mg/kg tablet group and 78.2% in the 12+4 mg/kg tablet group.

The PCR-corrected ACPR at Day 42 was 100% in the 6+2 mg/kg and 12+4 mg/kg tablet groups, 88.9% in the 9+3 mg/kg tablet group, and 92.9% in the 9+3 mg/kg granule group.

Through Day 42, 2 patients had *P. falciparum* recrudescence (at Day 35 and Day 36 in the 9+3 mg/kg tablet group and in the 9+3 tablet group) and 11 patients were reported as new-infections (3 prior Day 28 and 8 after Day 28) 3 in the 6+2 mg/kg dose, 5 in the 9+3 mg/kg tablets, 2 in the 12+4 mg/kg tablets, and one in the 9+3 mg/kg granules.

The median time to parasite clearance (per protocol analysis) was longer in the subjects treated with 6+2 mg/kg tablets and with 9+3 mg/kg tablets: i.e. 16.4 hours 16.1 hours respectively as compared to 8.1 hours observed in subjects treated with 12+4 mg/kg tablets, and 8.3 hours in subjects treated with 9+3 mg/kg granules.

Median fever clearance time was between 8.2 hours and 8.6 hours in all treatment groups.

The number of subjects with gametocytes was too low to derive any conclusive observation on the incidence rate of gametocytes. Seven subjects in total had *P. falciparum* gametocytes during this study. In 4 subjects, the gametocytes were present at baseline (complete clearance occurred on Day 22 and Day 14 in the 6+2 mg group, 32 hours after the first dose in the subject in the 9+3 mg granules, and on Day 14 in the subject treated with 12 +4 mg/kg), while 3 subjects (2 in the 6:2 mg group and one in the 9+3 mg group) had gametocytes that emerged only after baseline.

The bioavailability profile of granule and tablets of group B tablets, and group D granules was not shown, based on sparse available data on plasmatic measurement. However, this study was not properly designed to assess bioequivalence between tablets and granules. Of note, the dosing range covered in group B and D is not the same as the dosage forms were different. Moreover, the dosage form of the tablets doesn't correspond to the "to be marketed tablets" nor to the tablet used in the phase III clinical. No conclusion on any bioequivalence between tablets and granules can be drawn from this study.

In this study, the mean half-life of pyronaridine ranged from 6.6 (±2.0) to 9.0 (±2.5) days after oral administration.

The PA fixed combination was well tolerated at doses up to PP 12 mg/kg and AS 4 mg/kg and no difference could be observed in efficacy in the different dose groups, but no firm conclusion can be drawn regarding children dosing as this study was not specifically designed to assess efficacy.

2.5.2. Main studies

The applicant conducted 5 phase III clinical studies:

- 3 phase III clinical trials were conducted in uncomplicated *Plasmodium falciparum* malaria. Two of them used PA 180 mg:60 mg tablet formulation (SP-C-004-06 and SP-C-005-06) in adults and

children ≥ 20 kg body weight and 1 paediatric study used PA 60mg:20mg granule formulation (SP-C-007-07) in children younger than 12 years (weighing from 6 to 25 kg)

- 2 phase III studies were conducted in *Plasmodium vivax* malaria using PP-AS 180:60 mg tablets. Study SP-C-006-06 included children and adults from 7 to 60 years and ≥20 kg body weight. Due to slow recruitment, study SP-C-008-07 was terminated prematurely by the sponsor after 30 adults had been included

- ***Plasmodium falciparum*:**

General remarks

All *Plasmodium falciparum* studies were almost similarly designed as non inferiority studies.

The main differences between the studies was the blinding (open versus double-blind) and the comparator used i.e. mefloquine plus artesunate (MQ+AS) or artemether plus lumefantrine (AL).

The 2 phase III studies using tablets 180:60 mg included patients ≥20 kg body weight and studied the same PA 3 days course dosing regimen based on body weight.

The clinical phase III study SP-C-007-07 studied a granule formulation of PA 60:20 mg in children less than 12 years and weighing from 6 to 25 kg with a dosing regimen slightly different as compared to tablets. As granule formulation not the scope of the present Article 58 application, study P-007-07 is presented as supportive data only, providing a large amount of paediatric data.

For all *Plasmodium falciparum* studies, the primary efficacy end point was PCR-corrected ACPR (Adequate Clinical and Parasitological Response) at Day 28 which was defined as the absence of parasitaemia, irrespective of body temperature, without the patient meeting any of the criteria of early treatment failure, late clinical failure or late parasitological failure according to WHO (Guideline 2005):

- Early Treatment Failure (ETF):

Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitaemia

Parasitaemia on Day 2 post-dose higher than on Day 0 pre-dose count, irrespective of body temperature

Parasitaemia on Day 3 with fever (auxiliary temperature ≥ 37.5°C),

Parasitaemia on Day 3 ≥ 25 % of count on Day 0

- Late Clinical Failure (LCF) for the Day 28 endpoint:

Development of danger signs or severe malaria in the presence of parasitemia on any day between Day 4 and Day 28, without the patient previously meeting any of the criteria of early treatment failure,

Presence of parasitaemia and fever on any day from Day 4 to Day 28, without previously meeting any of the criteria of early treatment failure,

- Late Parasitological Failure (LPF) for the Day 28 endpoint:

Presence of parasitaemia on any day from Day 7 to Day 28 without fever, without previously meeting any of the criteria of early treatment failure or late clinical failure

PCR-corrected ACPR was the PCR genotyping-based correction used to distinguish new infections from recrudescence. Crude ACPR were not using the PCR correction to analyse re-appearance of parasitaemia.

Efficacy/safety criteria assessments were to be pursued till Day 42 follow-up.

The following definitions applied:

Safety Population (**Safety**): all randomised patients who received any amount of study medication. Patients will be analysed as treated.

Intent-To-Treat Population (**ITT**): all randomised patients who received any amount of study medication. Patients will be analysed as randomised. The ITT analysis will be regarded supportive of the EE analysis for the primary efficacy endpoint.

Originally, the primary end point of the 3 phase III studies in *Plasmodium falciparum* was based on **Day 28** assessment and an **Efficacy Evaluable (EE)** population was defined as those patients included in the **Intent to Treat (ITT)** population meeting pre-defined criteria at Day 28 as follows:

1. Having completed a full course of study medication and having known primary efficacy endpoint at Day 28. A patient will be excluded from the EE analysis if the parasite count is missing at Day 28 and no subsequent parasite count is available after Day 28 and the patient is not previously classified as treatment failure. This includes patients who discontinued from the study before Day X for any reason, as well as those who have had a re-infection before Day 28 and did not have any further parasite assessment.
2. No missed dose due to vomiting, as recorded on the 'study medication administration page' of the CRF, except at Day 28 where a patient may vomit after the first drug administration and have a repeat full dose. In this case, the repeated dose should not be vomited.
3. No concomitant medication (except paracetamol) that may interfere with the treatment outcome, up to Day 28. The list of forbidden medication is given as attachment to the protocol. A medical review will be performed to confirm the exclusion of a patient from the EE population.
4. No concomitant disease, such as Tuberculosis, HIV, severe URTI, gastrointestinal disease, etc…, which may interfere with the clear classification of the treatment outcome. A medical review of the diseases experienced will be performed to define the list of patients excluded from the EE population.
5. No major protocol violation. A major violation is any criteria that may affect the efficacy outcome of the patient. The list of all protocol violations will be assessed with regards to their impact (major/minor) prior to database lock.

A 28 day follow up was the standard advised in the WHO guidelines in place at the time that the studies were conducted. The CHMP raised the concern that 28 day follow–up was too short to allow proper comparisons of efficacy/failures of the treatments that all had a half life longer than one week. Subsequently, the applicant provided new analyses at Day 42 where the **EE population was newly defined by extending the initial Day 28 criteria for exclusion from EE population through Day 42.** As a result, the handling of missing data was reviewed and patients who discontinued the study before Day 42 without being previously classified as treatment failures were to be excluded from the Day 42 EE population due to missing endpoint data at Day 42. This additional analysis was considered to provide homogeneous handling of missing data throughout the 42 days period.

Invariably, patients with missing data were all rated as failures in the ITT population analyses.

All identified recrudescences were to be classified as failures both in the EE and ITT population.

Table 3: Handling of recrudescence and new infection for ITT and EE populations – original analysis Study SP-C-004-06 ; SP-C-005-06 and study SP-C-007-07 (RC = recrudescences, NI = new infections)

PCR-corrected analysis:	EE population *	ITT population
Day 14		
RC	Failure	Failure
NI before Day 14	Excluded	Failure
on Day 14	Excluded	Success
Day 28		
RC	Failure	Failure
NI before Day 28	Excluded	Failure
on Day 28	Success	Success
Day 42		
RC	Failure	Failure
NI before Day 28	Excluded	Failure
between Day 28 and Day 42	**Failure**	Failure
on Day 42	Success	Success
Crude analysis:	EE population **	ITT population
Day 14		
Re-appearance of parasites before or on Day 14	Failure	Failure
Day 28		
Re-appearance of parasites before or on Day 28	Failure	Failure
Day 42		
Re-appearance of parasites before or on Day 42	Failure	Failure

* The Efficacy Evaluable population was defined based on Day 28 and PCR corrected ACPR data. The same EE population was used at all time points and for both PCR corrected ACPR and Crude ACPR analyses
** Patients were excluded from the EE population if they had a new infection according to PCR Corrected ACPR before Day 28

Table 4: Handling of recrudescence and new infection for ITT and EE populations - Additional Analysis Study SP-C-004-06 and SP-C-005-06 (and Study SP-C-007-07)

PCR-corrected analysis:	EE population *	ITT population
Day 14		
RC	Failure	Failure
NI before Day 14	Excluded	Failure
NI on Day 14	Success	Success
Day 28		
RC	Failure	Failure
NI before Day 28	Excluded	Failure
NI on Day 28	Success	Success
Day 42		
RC	Failure	Failure
NI before Day 42	**Excluded**	Failure
NI on Day 42	Success	Success
Crude analysis:	EE population **	ITT population
Day 14		

Re-appearance of parasites before or on Day 14	Failure	Failure
Day 28		
Re-appearance of parasites before or on Day 28	Failure	Failure
Day 42		
Re-appearance of parasites before or on Day 42	Failure	Failure

* The Efficacy Evaluable population was defined based on PCR corrected ACPR data for each time point. The same EE population was used for both PCR corrected ACPR and Crude ACPR analyses
** Patients were excluded from the EE population at Day X (14, 28, 42) if they had a new infection according to PCR Corrected ACPR before Day X (14, 28, 42)

The efficacy results presented below are presented based on Day 42 end points in the ITT (all patients included) and in the revised EE populations.

Study SP-C-004-06: "A Phase III Comparative, Open-Label, Randomised, Multi-Centre, Clinical Study to Assess the Safety and Efficacy of Fixed Dose Formulation Oral Pyronaridine/Artesunate (180:60 mg Tablet) Versus Mefloquine (250 mg Tablet) Plus Artesunate (100 mg Tablet) in Children and Adult Patients With Acute Uncomplicated *Plasmodium falciparum* Malaria"

Methods

A multi-centre, randomised (2:1), controlled, open-label, 2 parallel groups, multicentre, non-inferiority phase III clinical trial conducted in 9 sites (Asia and Africa). The main objective of this clinical study was to compare the efficacy and safety of the fixed combination of PA with that of the combination of MQ + AS in children and adults with acute, uncomplicated *P. falciparum* malaria and to confirm that PA was non-inferior to MQ + AS in terms of efficacy.

Study Participants

Paediatric (≥20kg bodyweight, ≥3 years of age) and adult patients (≤90kg bodyweight, ≤60 years of age) suffering from acute, symptomatic, uncomplicated *P. falciparum* malaria were recruited from study sites South-East Asia (Thailand, Vietnam, Cambodia), India and Africa (Ivory Coast, Burkina Faso, Tanzania).

Patients were eligible to participate if they:

- Were ≥ 20kg and ≥3 years of age, and ≤90kg, and ≤60 years of age
- Had acute uncomplicated *P. falciparum* mono-infection defined by:
  - presence of fever (axillary/tympanic temperature ≥37.5°C or oral/rectal temperature ≥38°C) ***or*** documented history of fever in the previous 24 hours ***and***
  - positive microscopy of *P. falciparum* with parasite density between 1,000 and 100,000 asexual parasite count/µl blood
- Able to swallow oral medication, and able and willing to participate (the patient was to comply with all scheduled follow-up visits until day 42).

Written informed consent was obtained for each patient (if subject was unable to write, according to local ethical considerations witness consent was permitted).

Next to general exclusion criteria common for clinical trials, specific exclusion criteria were:

- Signs and symptoms of severe / complicated malaria requiring parenteral treatment according to the WHO criteria (*).

- Presence of mixed *Plasmodium* infection
- Severe vomiting (>3x in 24hrs prior to inclusion to study), severe diarrhoea (≥3 watery stools per day), or unable to tolerate oral treatment
- Known history or evidence of clinically significant disorders, such as:
    - cardiovascular (including arrhythmia, QTc interval ≥450 milliseconds);
    - respiratory (including active tuberculosis);
    - history of jaundice, hepatic, renal, gastrointestinal, immunological (including active HIV-acquired immune deficiency syndrome), neurological (including auditory), endocrine, infectious, malignancy, psychiatric (active depression, recent history of depression, generalised anxiety, psychosis, schizophrenia, or other major psychiatric disorders);
- History of convulsions or other abnormality (including recent head trauma).
- Presence of significant anaemia (Hb <8 g/dl)
- Presence of febrile conditions caused by diseases other than malaria
- Known history of hypersensitivity, allergic or adverse reactions to treatment
- Evidence of use of any other anti-malarial agent within 2 weeks prior to start of the study confirmed by positive urine test.
- Known active Hepatitis A IgM, Hepatitis B surface antigen or Hepatitis C antibody.
- Known seropositive HIV antibody.
- Liver function tests (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) >2.5 x upper limit of normal (ULN).
- Known significant renal impairment as indicated by serum creatinine >1.4 mg/dL
- Female subjects of childbearing potential must have been neither pregnant (as demonstrated by a negative pregnancy test) nor lactating, and must have been willing to take measures to not become pregnant during the study period

* Note : According to the Attachment 3 to the Clinical Study Protocol, severe manifestations of *P. falciparum* malaria are defined in adults and children as follows : clinical manifestation : prostration, impaired consciousness, respiratory distress (acidotic breathing), multiple convulsions, circulatory collapse, pulmonary oedema (radiological), abnormal bleeding, jaundice, haemoglobinurea; with laboratory findings : severe anaemia, hypoglycemia, acidosis, hyperlactataemia, hyperparasitaemia, renal impairment.

Treatments

Patients were randomised to receive either oral PA (180:60 mg fixed dose combination tablets), once daily for three consecutive days (0, 1, 2) ***or*** MQ (250mg tablets) plus AS (100mg tablets) once daily for three consecutive days (0, 1, 2). Treatment was administered by a third party investigator with (up to) 240 ml water; all tablets were to be swallowed whole. Dosing on Days 1 and 2 was to occur no less than 10 hours after the previous dosing.

Dosing of PA was based upon body weight (determined at screening):

- 20-25 kg, 1 tablet;
- 26-44 kg, 2 tablets;

- 45-64 kg, 3 tablets;
- 65-90 kg, 4 tablets;

The actual dose range for PA was 7.2:2.4 mg/kg to 13.8:4.6 mg/kg.

Dosing of MQ+AS was also based upon body weight, in accordance with WHO guidelines and current practice in countries:

- 20-40 kg, 1 tablet MQ & 1 tablet AS
- >40 kg, 2 tablets MQ & 2 tablets AS

The actual dosing range for MQ+AS was 5.6:2.2 mg/kg to 12.5:5.0 mg/kg.

If a subject vomited the first dose (Day 0) within 0 to 30 minutes of study drug administration, a repeat full dose was given. If this subject also vomited the study drug on either the second (Day 1) or third day (Day 2) of dosing, or if the subject vomited a re-administered dose on Day 0, the subject was not re-dosed, but was withdrawn from the study. A subject who was withdrawn due to vomiting was to receive rescue medication after completing the end-of-study assessments (Day 28 assessments).

Compliance was monitored via drug counts, drug accountability records and compliance assessments for each patient during monitoring visits.

Only paracetamol /acetaminophen (≤1 g) on day 0, 1 and 2 was allowed as co-medication. The use of any other medications, except for tetracycline as eye ointment, during the follow-up period was considered a violation of the protocol.

Objectives

The primary objective was to compare the efficacy and safety of the fixed combination of pyronaridine/artesunate ([PA] 180:60 mg combined tablets) with that of the combination of mefloquine (MQ) + artesunate (AS) in children and adults with acute, uncomplicated *Plasmodium falciparum* malaria.

No secondary objectives were defined.

At selected sites, the pharmacokinetics of pyronaridine and AS were characterised using a population pharmacokinetic approach.

Outcomes/endpoints

The primary efficacy end point was PCR-corrected ACPR (Adequate Clinical and Parasitological Response) at Day 28.

ACPR, ETF, LCF and LPF are defined as stated earlier (see "General remarks"). It also discusses that EE population was further re-defined by extending the initial Day 28 criteria for exclusion from EE population through Day 42.

Secondary efficacy endpoints:

- Proportion of subjects with PCR-corrected ACPR on Day 14
- (Non-PCR corrected) Crude ACPR on Day 14 and Day 28
- Parasite clearance time (PCT) defined as the time from first dosing to time of first blood draw with zero presence of asexual parasites for 2 consecutive negative readings taken between 7 and 25 hours apart.

- Fever clearance time (FCT) defined as the time from first dosing to first normal reading of temperature (<37.5°C taken axillary or tympanic; <38°C taken oral or rectal) for 2 consecutive normal temperature readings taken between 7 and 25 hours apart. The method of temperature measurement was to be the same (i.e., axillary, tympanic, oral, or rectal) for all measures in the same subject. Those subjects who were initially included on history of fever and who did not subsequently have a documented temperature reading ≥37.5°C (taken axillary or tympanic) or ≥38°C (taken oral or rectal) during the 24 hours following initial dosing were not included in this end point analysis.
- Proportion of subjects with cleared parasites at Days 1, 2, and 3.
- Proportion of subjects with fever cleared at Days 1, 2, and 3.

Sample size

The sample size was estimated assuming a PCR-corrected ACPR rate at Day 28 of 93% in both groups, and assuming a non-inferiority limit of 5%; then a sample size of 1140 evaluable subjects randomised in 2:1 ratio (380 subjects in the comparator MQ+AS group and 760 subjects in the PA group) was estimated to provide 90% power to demonstrate non-inferiority of PA compared to the comparator MQ+AS, using a 2-sided 95% CI for the difference in PCR-corrected ACPR response rate at Day 28.

Assuming a dropout rate of 10%, a total of 1269 subjects were to be randomised to the study (423 in the comparators group and 846 in the PA group). Sample size estimation was performed using nQuery statistical software i.e. Newcombe-Wilson score method.

The study was to be randomised, with a maximum of 200 subjects to be included per site.

Randomisation

Patients were randomised in a 2:1 ratio to receive either PA or MQ+AS according to a randomisation scheme. Patients were assigned in ascending order a randomisation number according to the order recruited.

Blinding (masking)

Investigators were blinded to treatment, as a third-party investigator who was made aware of treatment allocation administered study drugs. All study drugs were presented in identical external packaging.

Statistical methods

The EE analysis was considered the primary efficacy analysis. The primary efficacy analysis tested the non-inferiority of the PA group compared to the comparator group with regard to the PCR-corrected ACPR response rate at Day 28 using the 2-sided 95% confidence interval (CI) (Newcombe-Wilson score method without continuity correction) and a 5% non-inferiority margin.

Non-inferiority was demonstrated if the lower limit of this 2-sided 95% CI for the difference in PCR-corrected ACPR response rates at Day 28 was not lower than -5%.

For the purposes of the additional analyses requested by the CHMP, the EE population definition provided in the Amended Statistical Analysis Plan dated 06 Jan 2009 was amended to define the Day 42 EE population. This population has now been redefined as follows:

1. Having completed a full course of study medication and having known primary efficacy endpoint at Day **42**. A patient will be excluded from the EE analysis if the parasite count is missing at Day 42 and no subsequent parasite count is available after Day **42**, and the patient is not previously classified as treatment failure. This includes patients with missing Day **42** parasite count, who discontinued from the study before Day 42 for any reason, as well as those who have had a re-infection before Day 42 and did not have any further parasite assessment.
2. No missed dose due to vomiting, as recorded on the 'study medication administration page' of the CRF, except at Day 0 where a patient may vomit after the first drug administration and have a repeat full dose. In this case, the repeated dose should not be vomited.
3. No concomitant medication (except paracetamol) that may interfere with the treatment outcome, up to Day **42**. The list of forbidden medication is given in attachment 6 of the protocol. A medical review will be performed to confirm the exclusion of a patient from the EE population.
4. No concomitant disease, such as Tuberculosis, HIV, severe URTI, gastrointestinal disease, etc…, which may interfere with the clear classification of the treatment outcome. A medical review of the diseases experienced will be performed to define the list of patients excluded from the EE Day 42 population.
5. No major protocol violation. A major violation is any criteria that may affect the efficacy outcome of the patient. The list of all protocol violations will be assessed with regards to their impact (major/minor) prior to database lock.

A patient who discontinued from the study before Day 42 for any reason, who has missing Day 42 parasite count and no subsequent parasite count is available after Day 42, and the patient is not previously classified as treatment failure is excluded from the EE Day 42 population.

A patient who has had a re-infection before Day 42 and did not have any further parasite assessment and the patient is not previously classified as treatment failure is excluded from the EE Day 42 population.

The definitions for EE Population at Day 28, ITT Population and Safety Population (SAP dated 06 January 2009) remained unchanged

Results

Participant flow

A total of 1271 patients aged from 4 to 60 years were randomised in a 2:1 ratio (PA: n=848 patients and MQ+AS: n=423 patients) to receive for 3 consecutive days in an open label design either oral PA (180:60mg tablets) once a day (full 3 dose treatment: PP: 20.7 to 41.5 mg/kg; AS: 7.2 to 13.8 mg/kg) or MQ + AS (Artequin ® as co-blister pack of MQ 250-mg tablet and artesunate 100-mg tablet) once daily (full 3 dose treatment = MQ: 19.2 mg/kg to 37.5 mg/kg, AS : 7.5 mg/kg to 15 mg/kg).

The majority of subjects completed the 3 days treatment: 99.1% = 1260/1271 (PA group: 99.3% = 842/848; MQ+AS group: 98.8% = 418/423) and 85.0% (1080/1271) completed the study (PA group: 85.3% (723/848); MQ+AS: 84.4 % (357/423).

In other words, the rate of patients who did not complete the 3 days treatment was low 0.8% (11/1271 patients) and similar between the 2 groups: PA: 0.7% (6/848); MQ+AS: 1% (5/423). Among them, one from MQ+AS group was related to cerebral malaria after first dose (rated as early

treatment failure). Overall, the rate of patients who prematurely discontinued the study (15%= 191/1272 patients) was similar in each treatment group: PA: 14.8% (125/848); MQ+AS: 15% (66/423).

Re-appearance of *P. falciparum* (4.6% i.e.: PA: 4%; MQ+AS: 5.9%), *P. vivax* infections (2.4% i.e.: PA: 3.1%; MQ+AS: 0.9%) or lost of follow-up (5.8% i.e. PA: 5.8%; MQ+AS: 5.9%) were the most common reasons reported for withdrawal from the study.

Recruitment

The first patient was enrolled on the 25th January 2007, the last subject completed the study on the 2nd October 2008.

Conduct of the study

One amendment was made to the study protocol prior to the start of the study, (25-01-2007), and two amendments were made after the start of the study (12-06-2007 and 06-01-2009). The first amendment pertained mostly to administrative changes and clarifications. A major change was the inclusion of artesunate population PK analysis, next to the pyronaridine population PK analysis already included. The second amendment (12-06-2007) also pertained to mostly administrative changes, mainly resulting from the extension of the study to include African countries. The last amendment concerns the SAP, as it had been decided to combine the subgroup categories for age '5 to 12 years of age' with '< 5 years of age' due to a too small number of patients in the latter category.

Baseline data

The majority of subjects were male (75.8% patients) from Asian/Oriental sites (81.3%) : 47.2% at 2 sites in Thailand (Mae Sot : 23.6% and Mae Ramat: 23.6%), 12.8% at 2 site in Vietnam (Choray : 9.8% and Nimpe: 3.0%), 16.6% at a site in Cambodia (Pailin), 4.6% at a site in India (Mangalore); and from African sites (18.7%): 6.1% at a site in Ivory Coast (Abidjan), 9.6%at a site in Burkina Faso (Bobo Dioulasso) and 3.0% at a site Tanzania (Bagamoyo).

Mean age was higher in Asia vs. Africa (27.9 years vs. 13.3 years), as was mean weight (50 kg vs. 36.87 kg). No patient was less than 4 years old or less than 20 kg. 15% were aged between 5 to 12 years (PA group: 122 patients) and 85% were > 12 years old.

Outcomes and estimation

See also Tabular Summary – Table 15

Table 5: Day 42 PCR-corrected ACPR in the EE population and the ITT population Study SP-C-004-06

	EE population		ITT population	
	Pyronaridine/Artesunate N=[698] n (%)	**Mefloquine + Artesunate N=[339] n (%)**	**Pyronaridine/ Artesunate N=[848] n (%)**	**Mefloquine + Artesunate N=[423] n (%)**
Patients excluded from the EE population :	150 (17.9%)	84 (19.8%)	**NA**	**NA**
PCR-corrected ACPR on Day 42				
Available observations	698 (100%)	339 (100%)	848 (100%)	423 (100%)
Number of patients cured	661	329	705	355
Cure rate (%)	94.7	97.1	83.1	83.9

95% CI*	92.8;96.2	94.6;98.6	80.4;85.6	80.1;87.3
Between group comparison				
Difference	-2.4		-0.8	
95% CI**	-4.7;0.4		-4.9;3.7	
Conclusion***	Non-inferiority		Non-inferiority	
P-value****	0.088		0.722	
Number of treatment failure	37 (5.3%)	10 (2.9%)	143 (16.9%)	68 (16.1%)
Early treatment failure	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
Late clinical failure	3 (0.4%)	0 (0.0%)	5 (0.6%)	0 (0.0%)
Late parasitological failure	34 (4.9%)	9 (2.7%)	39 (4.6%)	12 (2.8%)
Unknown (missing data) (a+b)	0 (0.0%)	0 (0.0%)	99 (11.7%)	55 (13.0%)
a) Previous New Infection	*0 (0.0%)*	*0 (0.0%)*	*32 (3.8%)*	*20 (4.7%)*
b) Other	*0 (0.0%)*	*0 (0.0%)*	*67 (7.9%)*	*35 (8.3%)*

ACPR = adequate clinical and. parasitological response, EE = efficacy evaluable, ITT = intent to treat, PCR = polymerase chain reaction
Note:Percentages are based on available observations
Patients who discontinued treatment due to an adverse event were classified as Early Treatment Failures according to a medical review.
* Exact two-sided 95% Confidence Interval (Pearson-Clopper)
** The two-sided Confidence Interval for between group comparison was calculated using Newcombe-Wilson method
*** Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -5%
**** Two-sided Chi-square test for superiority (performed only when non-inferiority had been demonstrated)

Figure 1: ACPR (PCR-corrected) on Days 14, 21, 28, 35, and 42 – ITT Population SP-C-004-06

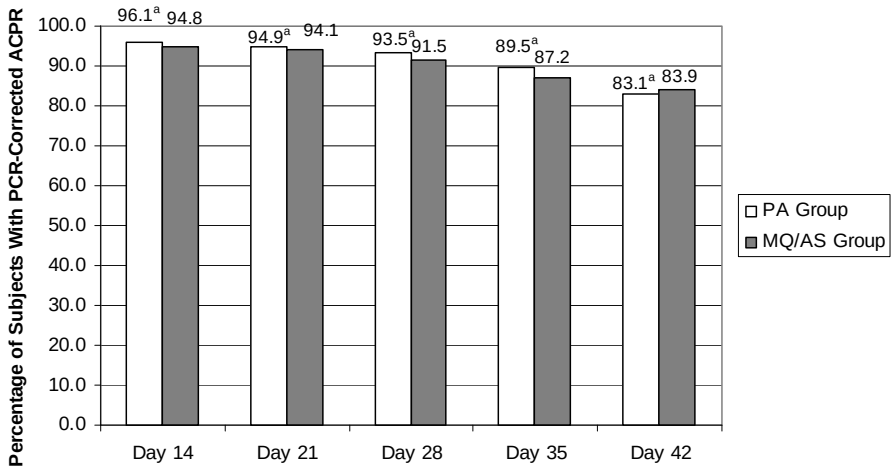


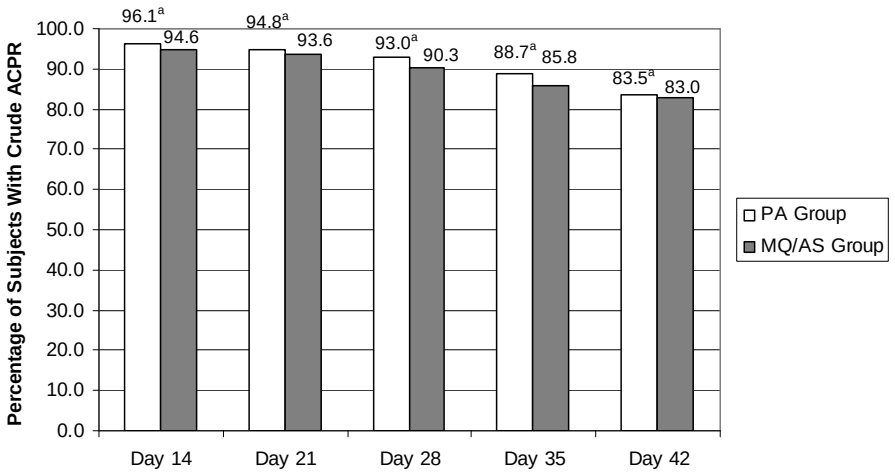
Table 6: Day 42 Crude ACPR in the EE population and the ITT population- Study SP-C-004-06

	EE population		**ITT population**	
	Pyronaridine/Artesunate N=[721] n (%)	**Mefloquine + Artesunate N=[355] n (%)**	**Pyronaridine/ Artesunate N=[848] n (%)**	**Mefloquine + Artesunate N=[423] n (%)**
Patients excluded from the EE population :	127 (15%)	68 (16%)	**NA**	**NA**
Crude ACPR on Day 42				
Available observations	721 (100%)	355 (100%)	848 (100%)	423 (100%)
Number of patients cured	662	325	708	351
Cure rate (%)	91.8	91.5	83.5	83.0
95% CI*	89.6;93.7	88.2;94.2	80.8;85.9	79.1;86.4
Between group comparison				
Difference	0.3		0.5	

95% CI**	-3.1;4.1		-3.7;5.0	
Conclusion***	Non-inferiority		Non-inferiority	
P-value****	0.881		0.818	
Number of treatment failures	59 (8.2%)	30 (8.5%)	140 (16.5%)	72 (17.0%)
Early treatment failure	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
Late clinical failure	12 (1.7%)	1 (0.3%)	14 (1.7%)	1 (0.2%)
Late parasitological failure	38 (5.3%)	26 (7.3%)	41 (4.8%)	30 (7.1%)
Unknown (missing data) (a+b)	9 (1.2%)	2 (0.6%)	85 (10.0%)	40 (9.5%)
a) Previous New Infection	*0 (0.0%)*	*0 (0.0%)*	*10 (1.2%)*	*3 (0.7%)*
b) Other	*9 (1.2%)*	*2 (0.6%)*	*75 (8.8%)*	*37 (8.7%)*

ACPR = adequate clinical and. parasitological response, EE = efficacy evaluable, ITT = intent to treat, PCR = polymerase chain reaction
Note: Percentages are based on available observations
Patients who discontinued treatment due to an adverse event were classified as Early Treatment Failures according to a medical review.
* Exact two-sided 95% Confidence Interval (Pearson-Clopper)
** The two-sided Confidence Interval for between group comparison was calculated using Newcombe-Wilson method
*** Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -5%
**** Two-sided Chi-square test for superiority (performed only when non-inferiority had been demonstrated)

Figure 2: ACPR (Crude) on Days 14, 21, 28, 35, and 42 – ITT Population SP-C-004-06



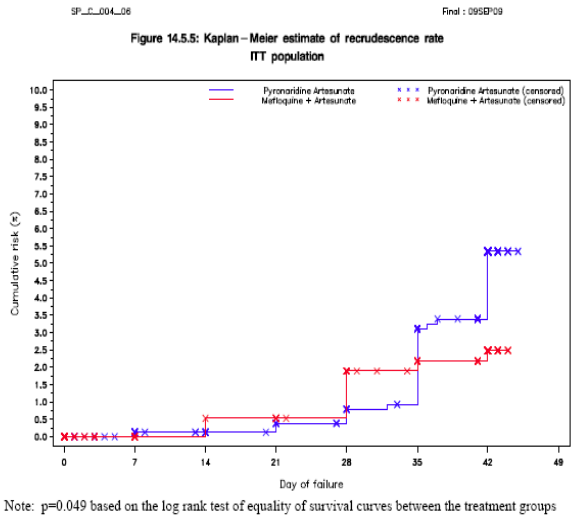
Note: The Day 21 and Day 35 analyses were performed post hoc.
a) Non-inferiority of PA to MQ + AS was concluded because the lower limit of the 2-sided 95% CI for the difference was >-5%.

Ancillary analyses

Recrudescences Kaplan-Meier estimates:

Kaplan-Meier estimates showed a cumulative risk of recrudescences not statistically different between PA and MQ+AS groups through Day 28 but it was increased in the PA group as compared to MQ+AS through Day 42 : PA: 5.3 % vs. MQ+AS : 2.5%. (log rank test p=0.049). There was no statistically significant difference in the rate of new infections (any species) between the PA and MQ+AS groups based on Kaplan-Meier estimates through Day 42 (p= 0.170).

Figure 3



In this study, non-inferiority is shown as compared to MQ+AS through Day 42 with respect to ACPR in all analyses (PCR-corrected and crude, EE and ITT population).

The rate of treatment failures (PCR-corrected) appears slightly higher in the PA group as compared to MQ+AS group i.e. 5.3% vs. 2.9 % respectively in the EE population.

Parasitic clearance time:

Pyronaridine/artesunate and MQ+AS were rapidly effective on parasitemia. Parasite count (*P. falciparum* asexual forms) decreased rapidly (during the first 16 hours) in both the PA and MQ+AS groups; time to parasite clearance was not statistically significantly different between the 2 groups. Median time to parasite clearance was 31.7 and 32.0 hours in the PA and MQ + AS groups, respectively.

Time to fever clearance was similar in the PA and MQ + AS groups but around 75% of the population was treated with antipyretic drugs.

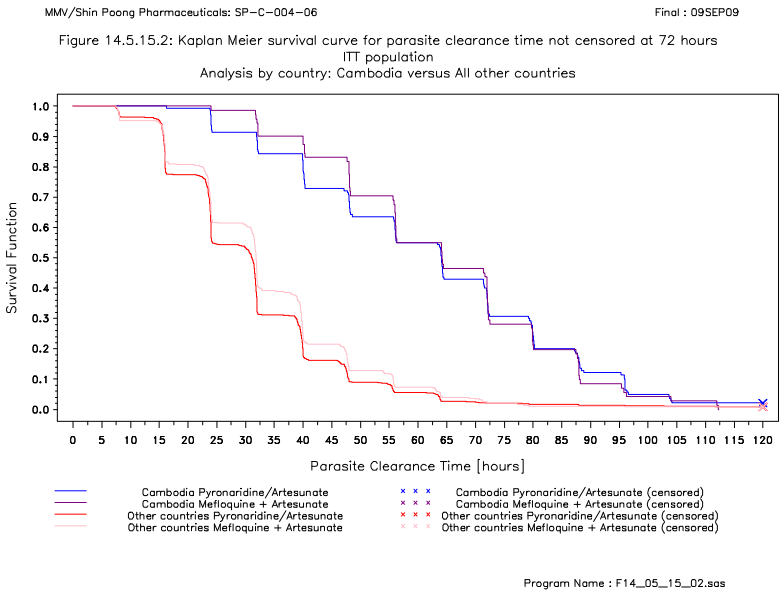
Cambodia (Pailin site) results:

Post hoc Kaplan-Meier analyses showed a higher rate of recrudescences at Day 42 in the PA group as compared to MQ+AS group in Cambodia (recrudescence rates: PA: 10.2%; versus MQ+AS = 0%, P=0.04). In the PA group, cumulative risk of recrudescences through Day 42 was statistically significantly greater among the 140 Cambodia PA patients (10.2%) as compared with the remaining 708 PA patients from all the other countries (4.7%) (p= 0.023). In the MQ+AS groups, no statistically significant difference between 71 MQ+AS Cambodia patients (4.7%) and the 352 MQ+AS patients from all the other countries (2.8%).

When data from Cambodia were excluded from the analysis there was no difference between treatment groups in *P. falciparum* recrudescence at Day 42. As Cambodia account for 24% of recrudescences with a proportion of patients of 20% out of the total size of study SP-C-004-06, the Cambodian results could have explained the higher rate observed in the global Day 42 population analysis.

A post-hoc Kaplan-Meier analyses showed that time to parasite clearance was statistically significantly longer in Cambodia as compared to all the other countries included in the study (log rank test p<0.001) both in the PA and MQ+AS groups (see figure below).

Figure 4: Kaplan-Meyer survival curve for parasite clearance time (ITT population)



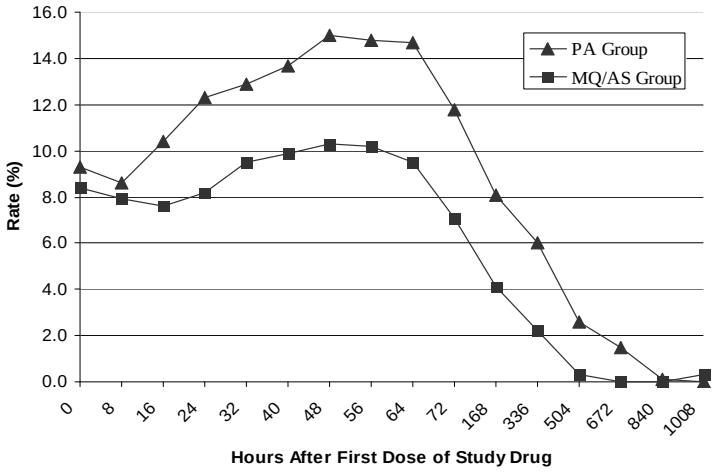
As expected the survival curves for parasite clearance time in this country were superimposable in the 2 treatment groups (not surprisingly as the earlier parasite clearance is driven by artesunate which is the compound used in both ACT groups compared in this study). Median time to parasite clearance in each treatment group in this study was approximately twice as long in Cambodia compared with all other countries (64 vs. 31-32 hours).

Although there is almost a 2-fold increase in median parasite clearance time in Cambodia compared with the other sites included, this difference was not reflected in a significant decrease in the clinical efficacy at Day 28. However, based on Day 42 efficacy results, it is pointed out that pyronaridine as partner to artesunate did not seem to show benefit as compared to mefloquine in this country where the emergence of *P. falciparum* resistance to anti-malarial drug treatment including ACT is of particular concern and where emerging lower susceptibility to artemisinins is recently being reported (ref: *Noedl H, N Engl J Med 2008; Dondorp AM, N Engl J Med 2009*).

Gametocytes:

The percentage of subjects with gametocytes was low at Day 0, hour 0 (EE population: PA: 70 patients= 9.3%, MQ+AS: 31 patients= 8.4%), rose through Hour 48, and gradually decreased to zero over time in both groups at Day 42. There is a larger increase in the % of patients with gametocytes in the PA arm following the start of treatment as compared to the MQ+AS arm. At Day 28, no patients from the EE population had gametocytes in the MQ+AS group and 11 patients (1.5%) were found with gametocytes in the PA group. At day 35 only one patient had gametocytes in the PA group and none had gametocyte in the MQ+AS group. At Day 42, one patient in the MQ+AS group was found with gametocytes. Although, the time to clearance of gametocytes is presented by the applicant as not statistically significant between the 2 groups within the first 72 hours (i.e. over 3 days after the treatment is started), the carriage of gametocytes appears longer in the PA group as compared to the MQ+AS group.

Figure 5: Percentage of Subjects With Gametocytes Over Time – EE Population SP-C-004-06



Study SP-C-005-06: "A Phase III Comparative, (Double-Blind, Double-Dummy), randomised, Multi-Centre, Clinical Study to Assess the Safety and Efficacy of Fixed Dose Formulation of Oral Pyronaridine/Artesunate Tablet (180:60 mg) Versus Coartem (Artemether /Lumefantrine) in Children and Adult Patients With Acute Uncomplicated *Plasmodium falciparum* Malaria"

Methods

A multi-centre, controlled, randomised, double blinded, double dummy, 2 parallel groups, non-inferiority phase III clinical trial conducted at 10 sites (Africa and South-East Asia). The study report states that the first patient was enrolled on 18 January 2007 and the last patient completed on 4 April 2008.

Study Participants

Paediatric (≥20kg bodyweight, ≥3 years of age) and adult patients (≤90kg bodyweight, ≤60 years of age) suffering from acute, symptomatic, uncomplicated *P. falciparum* malaria were recruited from study sites South-East Asia (Indonesia, The Philippines) and Africa (Senegal, The Gambia, Ghana, Kenya, Democratic Republic of Congo, Mali, Mozambique).

Exclusion criteria were identical to study SP-C-004-06.

Treatments

Patients were randomised to receive either oral PA (180:60-mg tablets) once daily plus artemether/lumefantrine (AL) placebo (twice daily) for 3 consecutive days (Days 0, 1, and 2) ***or*** AL twice daily plus PA placebo (once daily) for 3 consecutive days (Days 0, 1, and 2). Study drug and comparator drugs were given to each subject by the Third Party Investigator, with up to 240 ml (full glass) water (150 ml for children).

Dose was based on body weight (determined at screening) for both PA combination and AL.

For PA:

- 20-25 kg, 1 tablet;
- 26-44 kg, 2 tablets;
- 45-64 kg, 3 tablets;
- 65-90 kg, 4 tablets;

For AL:

- 20-24 kg, 2 tablets;
- 25-34 kg, 3 tablets;
- 35-90 kg, 4 tablets.

If a subject vomited within 0 to 30 minutes of receiving the first dose, a repeat full dose was given. If this subject also vomited during any subsequent dosing (second dose of AL on Day 0 and any other doses on Day 1 and Day 2), or if the subject vomited a re-administered dose on Day 0, the subject was not re-dosed, but was withdrawn from the study. A subject who was withdrawn due to vomiting was to receive rescue medication after completing the end-of-study assessments.

Compliance was monitored via drug counts, drug accountability records and compliance assessments for each patient during monitoring visits.3.

Concomitant medication

Paracetamol/acetaminophen (≤1 g) was allowed to treat fever >38.0°C. Concomitant disease and/or AEs requiring treatment could have been treated according to local practise. The use of antimalarials or antibiotics (with antimalarial activity) during the study, except for tetracycline as eye-ointment, was considered a violation of the protocol.

Objectives

The main objectives of this clinical study were to compare the efficacy and safety of the fixed combination of pyronaridine:artesunate tablet (PA : 180:16 mg) with that of artemether:lumefantrine (AL) combination (Coartem® 20:120 mg tablets) in children and adults with acute, uncomplicated P. falciparum malaria.

Outcomes/endpoints

The primary efficacy endpoint for the study is the proportion of patients with PCR-corrected ACPR on Day 28.

ACPR, ETF, LCF and LPF are defined as stated earlier (see "General remarks"). It also discusses that EE population was further re-defined on CHMP request, by extending the initial Day 28 criteria for exclusion from EE population through Day 42.

Secondary efficacy endpoints were identical to those defined for study SP-C-004-06.

Sample size

Sample size determination was identical as described for study SP-C- 004-06.

Randomisation

Patients who met all entry criteria and no exclusion criteria were randomised in a 2:1 ratio to receive either PA or AL according to the randomisation scheme provided by the Sponsor. Patients were assigned, in ascending order, a randomisation number according to the order recruited.

Blinding (masking)

The study was designed as a double-blind trial, using a double-dummy approach.

Statistical methods

Three different analysis populations were defined: Safety, ITT and EE population. For a definition of these populations please refer to "General remarks".

For the purposes of the additional analyses requested by the CHMP, the EE population definition provided in the Statistical Analysis Plan was amended to define the Day 42 EE population.

Results

Participant flow

A total of 1272 subjects aged from 5 years to 60 years were randomised in a 2:1 ratio (n=849 patients in the PA group and n=423 patients in the AL group) to receive for 3 consecutive days in a double dummy design, either oral PA (180:60mg tablets) once a day (full 3 dose treatment: PP: 20.7 to 41.5 mg/kg; AS: 7.2 to 13.8 mg/kg) or AL (Coartem® 20:120 mg tablets), twice a day (full 6-doses treatment = artemether : from 15.6 to 43.2 mg/kg; lumefantrine: from 31.8 to 86.4 mg/kg).

The majority of subjects completed the 3 days treatment: 97.3% = 1238/1372 (PA group: 97.1% = 824/849; AL group: 97.9% = 414/423) and 86.3% (1098/1272) completed the study (PA group: 88.5% (751/849); AL: 82.0 % (347/423). Conversely, 2.7% (34/1272 patients) discontinued the 3 dose treatment slightly more frequently in the PA group: 2.9%= 25/849 patients than in the AL group: 2.1% = 9/423 patient. The applicant has reviewed the cases of treatment withdrawals, and finally, among the 28 patients (PA: 21, AL: 8) withdrawn due to vomiting, 8 patients (of whom one case due to cerebral malaria) and 2 patients can be recognised as treatment failures in the PA and AL groups, respectively. The description provided by the applicant does not specify the age of the patients. Unfortunately without susceptibility data and assessment of plasmatic levels at the time of withdrawal, it can not be established whether those failures would have been related to strain resistance to both active drugs or to sub-therapeutic plasma levels.

Overall, 13.7% (174/1272 patients) prematurely discontinued the study more frequently in the AL group: 18.0% (=76/423 patients) than in the PA group 11.5% (98/849). Re-appearance of *P. falciparum* (or *P. vivax* infection) or adverse events were the most frequent reasons reported for withdrawal from the study (6.4%, and 2.2% respectively).

In the newly provided defined Day 42 EE analysis, 15.3% patients were excluded from the PCR-corrected Day 42 EE population, PA: 13.1% and AL: 19.6% of patients.

Recruitment

The first patient was enrolled on 18 January 2007 and the last patient completed on 4 April 2008.

Conduct of the study

One amendment was made to the study protocol prior to the start of the study, (13-02-2007), consisting of administrative changes and clarifications and the addition of 2 countries to the final protocol (dd 06-09-2006).

Contrary to the SAP, a summary of shifts in physical examination from baseline was not provided for each post-baseline assessment visit. In addition, the number of subjects with a count of 0, 1, 2, 3, 4, and >4 symptoms present at each assessment visit was not summarised.

A logistic regression analysis was planned to be performed to assess the treatment-by-centre interaction. Considering the high PCR-corrected ACPR rate, it was, however, not possible to assess the interaction. As a consequence, the logistic model only included the following covariates: treatment group, age category (<5 years, 5-12 years, >12 years), gender, actual drug dosing (7.2:2.4 to 8.5:2.8 mg/kg, >8.5:2.8 to 9.5:3.2 mg/kg, >9.5:3.2 to 11:3.7 mg/kg, and >11:3.7 to 13.8:4.6 mg/kg), and previous episode of malaria (yes or no)

Several Post Hoc analyses were performed.

Baseline data

The majority of subjects were from Africa (84.9%): 23.4% at a site in Democratic Republic of Congo (Kinshasa), 8.3% at a site in Gambia (Farafeni), 0.6% at a site in Ghana (Kumasi), 10.4% at a site in Kenya (Siaya District), 15.6% at a site in Mali (Bougoula), 10.5% at a site in Mozambique (Maputo), and 16.2% at a site in Senegal (Dakar). The remaining 15.1% were from 2 sites in Indonesia (Maumere 3.2% and Jayapura 3.8%) and a site in Philippines: 8.1% (Puerto Princesa).

Most subjects were male (56.7%) and Black (84.9%); mean age was 17.5 years higher in Africa than in Asia (26.1 years vs. 16.0 years). No patients were less than 5 years 44% were aged between 5 to 12 years (PA= 378 patients), 56% being aged more than 12 years. Body weight ranged from 20 kg to 89.5 kg.

Outcomes and estimation

See also Tabular Summary – Table 16

The efficacy results are as follows:

Table 7: Day 42 PCR-corrected ACPR in the EE population and the ITT population SP-C-005-06

	EE population		**ITT population**	
	Pyronaridine Artesunate N=[746] n (%)	**Artemether Lumefantrine N=[342] n (%)**	**Pyronaridine Artesunate N=[849] n (%)**	**Artemether Lumefantrine N=[423] n (%)**
Patients excluded from the EE population :	103 (12.1%)	81 (19.1%)	**NA**	**NA**
PCR-corrected ACPR on Day 42				
Available observations	746 (100%)	342 (100%)	849 (100%)	423 (100%)
Number of patients cured	729	337	746	346
Cure rate (%)	97.7	98.5	87.9	81.8
95% CI*	96.4; 98.7	96.6; 99.5	85.5; 90.0	77.8; 85.4
Between group comparison				
Difference	-0.8		6.1	
95% CI**	-2.4; 1.3		1.9; 10.5	
Conclusion***	Non-inferiority		Non-inferiority	

P-value****	0.374		0.003	
Number of treatment failure	17 (2.3%)	5 (1.5%)	103 (12.1%)	77 (18.2%)
Early treatment failure	8 (1.1%)	2 (0.6%)	8 (0.9%)	2 (0.5%)
Late clinical failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Late parasitological failure	9 (1.2%)	3 (0.9%)	9 (1.1%)	3 (0.7%)
Unknown (missing data) (*a+b*)	0 (0.0%)	0 (0.0%)	86 (10.1%)	72 (17.0%)
a) Previous New Infection	*0 (0.0%)*	*0 (0.0%)*	*33 (3.9%)*	*37 (8.7%)*
b) Other	*0 (0.0%)*	*0 (0.0%)*	*53 (6.2%)*	*35 (8.3%)*

ACPR = adequate clinical and. parasitological response, EE = efficacy evaluable, ITT = intent to treat,
PCR = polymerase chain reaction
Note: Percentages are based on available observations
Patients who discontinued treatment due to an adverse event were classified as Early Treatment Failures according to a medical review.
* Exact two-sided 95% Confidence Interval (Pearson-Clopper)
** The two-sided Confidence Interval for between group comparison was calculated using Newcombe-Wilson method
*** Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -5%
**** Two-sided Chi-square test for superiority (performed only when non-inferiority had been demonstrated)

Figure 6: ACPR (PCR-corrected) on Days 14, 21, 28, 35, and 42 – ITT Population SP-C-005-06

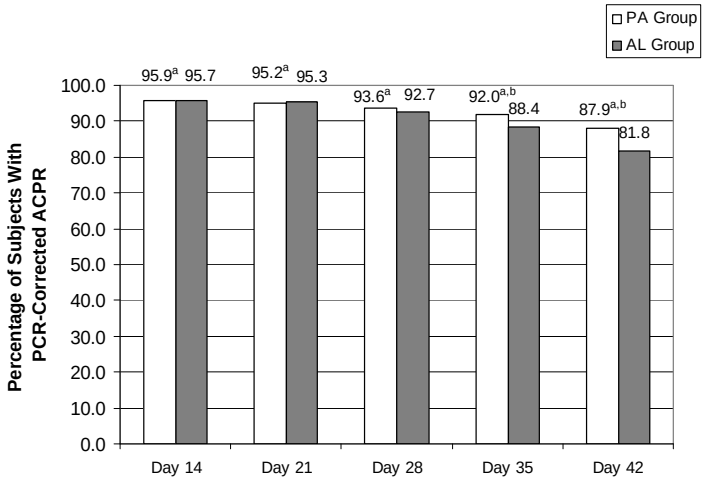


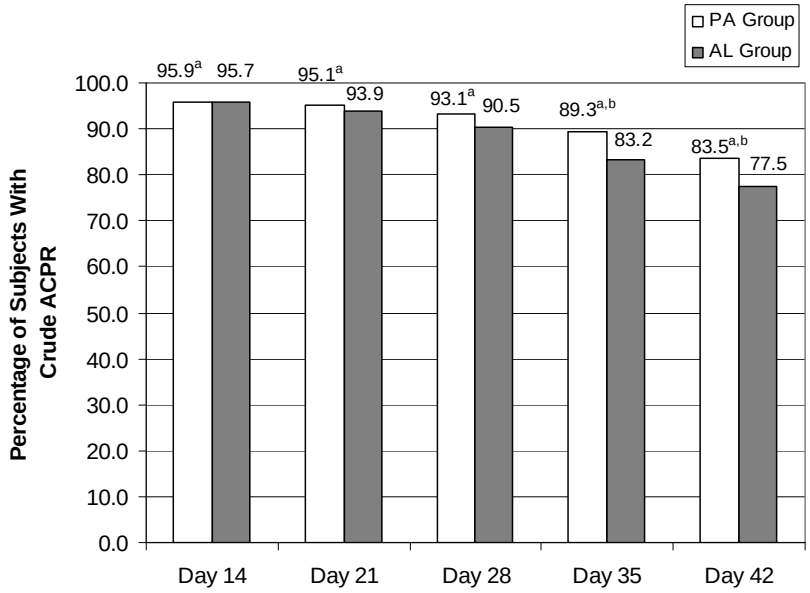
Table 8- Day 42 Crude ACPR in the EE population and the ITT population SP-C-005-06

	EE population		**ITT population**	
	Pyronaridine/Artesunate N=[779] n (%)	**Artemether/ Lumefantrine N=[379] n (%)**	**Pyronaridine/Artesunate N=[849] n (%)**	**Artemether/ Lumefantrine N=[423] n (%)**
Patients excluded from the EE population :	70 (8.2%)	44 (10.4%)	**NA**	**NA**
Crude ACPR on Day 42				
Available observations	779 (100%)	379 (100%	849 (100%)	423 (100%)
Number of patients cured	693	319	709	328
Cure rate (%)	89.0	84.2	83.5	77.5
95% CI*	86.5;91.1	80.1;87.7	80.8;85.9	73.3;81.4
Between group comparison				
Difference	4.8		6.0	
95% CI**	0.7;9.3		1.4;10.8	
Conclusion***	Non-inferiority		Non-inferiority	
P-value****	0.021		0.010	
Number of treatment failures	86 (11.0%)	60 (15.8%)	140 (16.5%)	95 (22.5%)
Early treatment failure	8 (1.0%)	2 (0.5%)	8 (0.9%)	2 (0.5%)

Late clinical failure	2 (0.3%)	9 (2.4%)	2 (0.2%)	9 (2.1%)
Late parasitological failure	76 (9.8%)	48 (12.7%)	77 (9.1%)	49 (11.6%)
Unknown (missing data)) (*a+b*)	0 (0.0%)	1 (0.3%)	53 (6.2%)	35 (8.3%)
a) Previous New Infection	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*
b) Other	*0 (0.0%)*	*1 (0.3%)*	*53 (6.2%)*	*35 (8.3%)*

ACPR = adequate clinical and. parasitological response, EE = efficacy evaluable, ITT = intent to treat, PCR = polymerase chain reaction
Note: Percentages are based on available observations
Patients who discontinued treatment due to an adverse event were classified as Early Treatment Failures according to a medical review.
* Exact two-sided 95% Confidence Interval (Pearson-Clopper)
** The two-sided Confidence Interval for between group comparison was calculated using Newcombe-Wilson method
*** Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -5%
**** Two-sided Chi-square test for superiority (performed only when non-inferiority had been demonstrated.

Figure7: ACPR (Crude) on Days 14, 21, 28, 35, and 42 – ITT Population SP-C-005-06



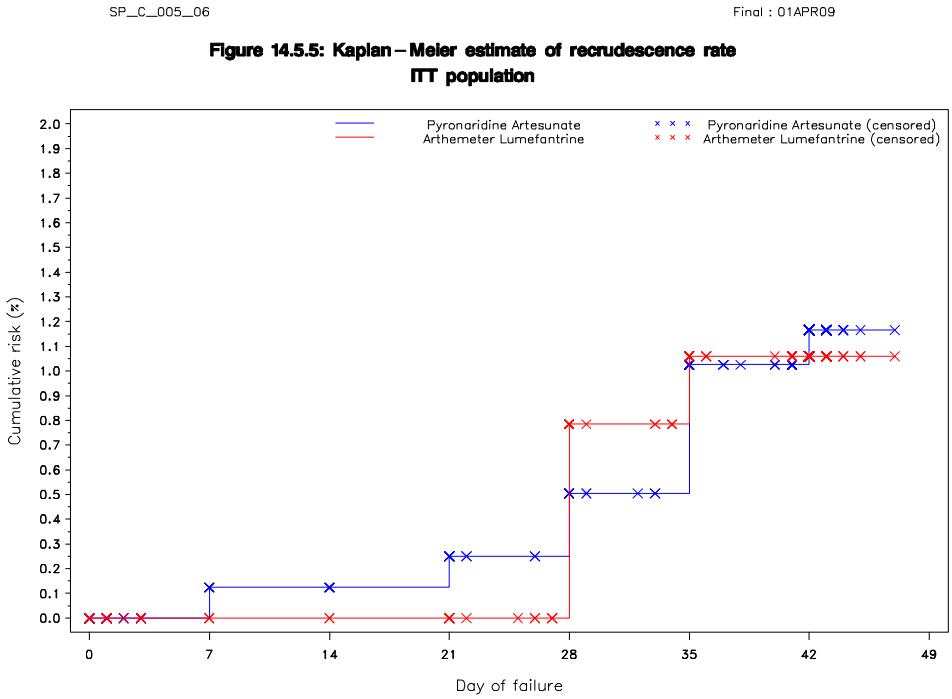
Note: The Day 21 and Day 35 analyses were performed post hoc.
a) Non-inferiority of PA to AL was concluded because the lower limit of the 2-sided 95% CI for the difference was >-5%.
b) Superiority of PA over AL was concluded.

Ancillary analyses

Recrudescences Kaplan-Meier estimates:

No statistically significant difference between the PA and AL groups was observed in the Kaplan-Meier estimate of cumulative risk of recrudescences through Day 42 (p=0.895); (Day 28 (p=0.578)).

Figure 8



Note: p=0.859 based on the log rank test of equality of survival curves between the treatment groups

In study SP-C-005-06, non inferiority is consistently shown as compared to AL with respect to Day 42 ACPR in all analysis (PCR-corrected and crude, EE and ITT populations). Rate of recrudescences and failures were similar in both groups.

Parasitic clearance time

Pyronaridine/artesunate and AL were both rapidly effective on parasitemia. Parasite count (*P. falciparum* asexual forms) decreased rapidly (during the first 16 hours) in both the PA and AL groups. The mean parasite count (*P. falciparum* asexual forms) over the 3 days treatment did not show any difference between the PA and AL groups.

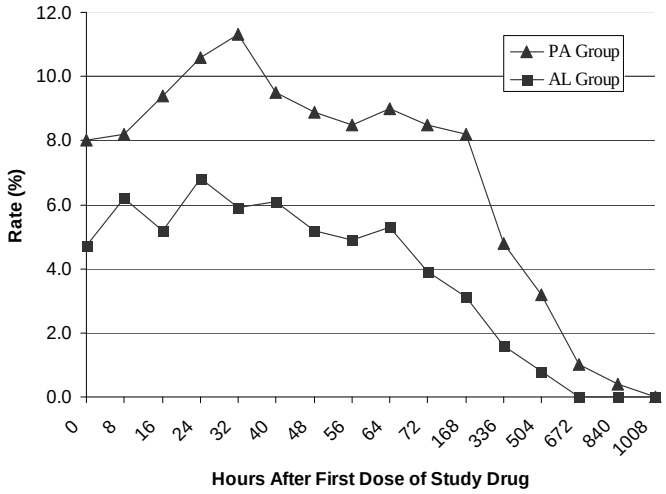
In the EE population 68.1% vs. 52.8% patients achieved parasite clearance 24 hours after the first dose in the PA and AL groups respectively. Median time to parasite clearance was 23.9 and 24.0 hours in the PA and AL groups, respectively.

No difference was observed on time to fever clearance between the groups, but the largest part of the population was treated with antipyretics.

Gametocytes:

The percentage of subjects with gametocytes was low at Day 0, hour 0 (EE population: PA:63 patients= 9.0%, AL: 18 patients= 4.7%), rose through Hour 48, and gradually decreased to zero over time in both groups at day 42. At Day 28, no patients from the EE population had gametocytes in the AL group and 8 patients (1%) were found with gametocytes in the PA group. At day 35, 3 patients had gametocytes in the PA group who decreased to 0 at Day 42. No gametocytes carriage is reported in the AL group at day 32 and 42. Although, the time to clearance is presented by the applicant as not statistically significant between the 2 groups within the first 72 hours (i.e. over 3 days after the treatment is started), the carriage of gametocytes appears longer in the PA group as compared to the AL group

Figure 9: Percentage of Subjects With Gametocytes Over Time – EE Population (42 Days) - SP-C-005-06



Study SP-C-007-07: "A Phase III Comparative, Open-Labelled, Randomised, Multi-Centre Clinical Study to Assess Safety and Efficacy of a Fixed Dose of Oral Pyronaridine/Artesunate Granule Formulation (60:20 mg) (Paediatric PYRAMAX) Versus Coartem (Artemether/Lumefantrine) Crushed Tablets in Infants and Children With Acute Uncomplicated *Plasmodium falciparum* Malaria

Methods

This was a multi-centre, controlled, randomised, open-label, 2 parallel groups, non-inferiority phase III clinical trial conducted at 7 sites (East, Central and West Africa and in Philippines).

Study Participants

Paediatric patients (≤12 years of age) suffering from acute, symptomatic, uncomplicated *P. falciparum* malaria were recruited from 7 investigative sites in Burkina Faso, the Democratic Republic of Congo, Gabon, The Ivory Coast, Kenya, Mali, and The Philippines.

Patients were eligible to participate if they:

- Were male or female, ≤12 years of age with a body weight ≥5 kg and <25 kg, with no clinical evidence of severe malnutrition, defined as a child whose weight-for-height is below -3 standard deviations or <70% of the median of the National Centre for Health Statistics/WHO normalised reference values.
- Had acute uncomplicated *P. falciparum* mono-infection defined by:
  - presence of fever (axillary temperature ≥37.5°C or oral/tympanic/rectal temperature ≥38°C) ***or*** documented history of fever in the previous 24 hours ***and***
  - positive microscopy of *P. falciparum* with parasite density between 1,000 and 100,000 asexual parasite count/µl blood

- Were able to swallow oral medication, and able and willing to participate (the patient was to comply with all scheduled follow-up visits until day 42).

Written informed consent was obtained for each patient (if subject was unable to write, according to local ethical considerations witness consent was permitted).

Exclusion criteria were identical to those of trials SP-C-004-06 and SP-C-005-06.

Treatments

Subjects were randomised to receive either oral PA granule formulation (60:20-mg granules sachets) once a day for 3 consecutive days (Days 0, 1, and 2) ***or*** AL (20:120-mg crushed tablets) twice a day for 3 consecutive days (Days 0, 1, and 2).

Subject weight recorded during the physical examination at screening was used to calculate the number of sachets/tablets to be administered per dose on all study days.

Subjects randomised to paediatric PA received between 1 and 3 sachets a day based on body weight as follows: ≥5-<9kg, 1 sachet; 9-<17 kg, 2 sachets; 17-<25 kg, 3 sachets. For subjects randomised to receive PA, dosing on the 2 subsequent days occurred no less than 10 hours after the previous dosing.

Subjects randomised to AL received 1 or 2 crushed tablets (each tablet contained 20 mg artemether and 120 mg lumefantrine) twice a day based on body weight as follows: ≥5-<15 kg, 1 tablet; 15-<25 kg, 2 tablets. Subjects randomised to receive AL crushed tablets received 2 administrations per day for each of the 3 treatment days. The Day 0 second dose occurred 8 hours after the first dose. The first dose on Day 1 occurred 24 hours after the Day 0 first dose. Dosing then occurred every 12 hours after the previous dosing for the last 3 doses (6 doses in total).

The PA and AL oral suspensions were prepared immediately before each administration. Water for dispersion and consumption following dosage administration must not have been carbonated.

Study drugs were given to each subject by the Third Party Investigator, with up to 150 mL (full glass) of liquid. Subjects were to take the medication in an upright position (seated or standing).

The qualitative and quantitative composition of the granule significantly differs from tablets. Based on the available data, no bioequivalence can be established between the two formulations.

Objectives

The main objectives of this clinical study were to demonstrate the efficacy of a fixed combination of PA granule formulation (60:20 mg) in children ≤12 years of age with acute, uncomplicated *P. falciparum* malaria by showing a PCR-corrected adequate clinical and parasitological cure rate of more than 90% on Day 28.

The secondary objectives were to compare the efficacy (non-inferiority) and safety of PA granule formulation compared to Coartem (i.e., the combination of artemether/lumefantrine [AL]) crushed tablets in a paediatric population and to assess the safety of PA granule formulation.

Outcomes/endpoints

The primary efficacy endpoint for the study was the proportion of subjects with PCR-corrected ACPR on Day 28.

ACPR, ETF, LCF and LPF are defined as stated earlier (see "General remarks"). It also discusses that EE population was further re-defined on CHMP request, by extending the initial Day 28 criteria for exclusion from EE population through Day 42.

Secondary efficacy endpoints were identical to those defined for study SP-C-004-06.

Sample size

For the primary objective, a total of 320 evaluable subjects in the PA group would provide 91% power to reject the null hypothesis H_0: cure rate at Day 28 is ≤90 % in favour of the alternative H_1: cure rate >90% (assuming an expected cure rate of 95%) using a 1-sided exact binomial test with a nominal significance level of 2.5%.

For the secondary objective: Assuming a cure rate on Day 28 of 95% in both treatment groups and assuming a non-inferiority limit of -10%, then a sample size of 480 evaluable subjects randomised in 2:1 ratio (320 subjects to PA and 160 to AL) would provide >99% power to demonstrate non-inferiority of PA compared to AL crushed tablets, using a 2-sided 95% confidence interval with normal approximation.

Assuming a dropout rate of 10%, a total of 534 subjects were to be enrolled in the study (356 subjects to PA and 178 to AL).

Randomisation

Subjects who met all entry criteria and no exclusion criteria were randomised in a 2:1 ratio to receive either PA granule formulation in sachet or AL crushed tablets according to the randomisation scheme provided by the sponsor. Subjects were assigned a randomisation number in ascending order and were allocated an individually numbered treatment pack. The study was randomised, with a maximum of 150 subjects to be included per site

Blinding (masking)

This study was open-label. However, the secondary packaging of the study medication was blinded in order to ensure a proper randomisation with no bias. Blinded subject pack labels included study number, drug names, randomisation number, batch number, expiration date, storage information, sponsor's name, and the information that the product was to be administered by study staff after randomisation only and only to be used for clinical study purposes. The sponsor remained blinded throughout the conduct of the trial. No code breaks were required during the course of the study.

Statistical methods

The EE analysis was considered the primary efficacy analysis. The primary efficacy analysis was repeated for the ITT population.

The secondary efficacy analysis tested the non-inferiority of PA compared to the AL group with regard to the PCR-corrected ACPR response rate on Day 28 using a 2-sided 95% confidence interval (Newcombe Wilson score method without continuity correction) and a 10% non-inferiority margin for the EE population. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval for the difference in 28-day PCR-corrected ACPR was not lower than -10%.

If non-inferiority of PA was demonstrated, the p-value associated with a superiority test was calculated based on a 2-sided Chi-Square test (assuming the estimated difference in response rates was in favour of the PA group). If the calculated p-value was <0.05, then the superiority of PA over AL was

statistically demonstrated. No multiplicity testing adjustment was required as this testing procedure corresponds to a closed test procedure.

The same statistical analysis was repeated for the 14-day PCR corrected ACPR and the crude 14-day and 28-day ACPR. It should be noted that subjects who discontinued from the study prior to Day 14 were excluded from the EE analysis.

The PCT and FCT were summarised using Kaplan-Meier estimates. Treatment group comparison of PCT and FCT was done by means of the log-rank test. Subjects who did not have (confirmed) parasite or fever clearance within 72 hours after the first dose of study drug were censored at that time point. The proportion of subjects with parasite clearance/fever clearance on Day 1 (24 hours after first dose), Day 2 (48 hours after first dose), and Day 3 (72 hours after first dose) was calculated using Kaplan-Meier estimates. The associated 2-sided 95% CI was also calculated.

Results

Participant flow

Table 9	PA n (%)	AL n (%)	Total n (%)
Subjects randomised	355	180	535
Subjects randomised but not treated	0	0	0
Subjects treated[a]	355 (100.0)	180 (100.0)	535 (100.0)
Subjects who completed treatment[b]	349 (98.3)	174 (96.7)	523 (97.8)
Subjects who completed study	274 (77.2)	142 (78.9)	416 (77.8)
Subjects who discontinued	81 (22.8)	38 (21.1)	119 (22.2)
Adverse event/SAE	6 (1.7)	3 (1.7)	9 (1.7)
Consent withdrawn	2 (0.6)	2 (1.1)	4 (0.7)
Lost to follow-up	6 (1.7)	1 (0.6)	7 (1.3)
Other (parasite re-appearance/malaria)	67 (18.9)	32 (17.8)	99 (18.5)

Note: Percentages are based on the number of randomised subjects.

a. Received ≥1 dose of study medication.

b. Received all 3 (PA group)/6 (AL group) planned doses of study medication.

A total of 535 patients were randomised aged less than 12 years were randomised in a 2:1 ratio (n= 355 to the PA group and n= 180 subjects to the AL group) to receive for 3 consecutive days in a open label design oral pyronaridine/artesunate (PA) (60mg:20 mg granules) once a day (full 3 dose treatment : PP: 21.6 to 40 mg/kg; AS: 7.52 to 13.5 mg/kg) or oral artemether/lumefantrine (AL) (Coartem 20:120 mg crushed tablets), twice a day (full 6-doses treatment from 8.4 to 24 mg/kg for artemether and from 51.6 to 144 mg/kg for lumefantrine).

The majority of subjects completed the 3 days treatment: 97.8% = 523/535 (PA group: 98.3% = 349/355; AL group: 96.7% = 174/180) and 77.8% (416/535) completed the study (PA group: 77.2% (274/355); AL: 78.9 % (142/180)).

In other words, 2.25% (12/535 patients) discontinued the 3 dose treatment slightly more frequently in the PA group: 3.4%= 6/355 patients as compared to the AL group: 1.4%= 6/180 patients and 22.7% (119/535 patients). Based on the reviewing of the individual cases performed by the applicant in the 6 PA and 6 AL patients who did not complete the treatment, 2 PA patients (and none in the AL group) were to be considered as early treatment failures. The description provided by the applicant does not specify the age of those patients. Unfortunately without susceptibility data and assessment of plasmatic levels at the time of withdrawal, it can not be established whether those failures would have been related to strain resistance to both active drugs or to sub-therapeutic plasmatic levels.

Overall, a rate of 22.2% patients discontinued the study with a similar frequency in each group: PA: 22.8%, AL 21.1%. Parasite re-appearance/malaria was the most common reason reported for withdrawal from the study (18.5%).

Recruitment

The study report states that first patient enrolled on 19 November 2007 and last patient completed on 15 September 2008.

Conduct of the study

There were no amendments to the original protocol (28 June 2007). There was 1 amendment to the original SAP (20 February 2009) that occurred after database lock.

Baseline data

The majority was black (96.1%) subject and from Africa: 96.3% (515/535): 5.2 at a site in Burkina Faso (Ouagadougou), 15.7% at a site in Democratic Republic of Congo (Kinshasa), 20.0% at a site in Ivory Coast (Abidjan), 16.1% at a site in Kenya (Siaya District), 24.3% at a site in Mali (Bougoula), 15.% at a site in Gabon (Lambarene) and 3.7% (21 patients) were from a site in Philippines (Puerto Princesa).

There were approximately equal percentages of male and female subjects and mean age was 5 years old with 43.4% of patients less than 5 years = 232/535 ; PA: 160, AL: 72. Thirteen (13) were aged less than 1 year (PA: 10; AL= 3). All were less than 25 kg body weight.

Outcomes and estimation

See also Tabular Summary – Table 18

Efficacy data (Day 42) are presented as follows:

Table 10: Day 42 PCR-corrected ACPR in the EE population and the ITT population- SP-C-007-07

	EE population		**ITT population**	
	Pyronaridine/Artesunate N=[275] n (%)	**Artemether/Lumefantrine N=[139] n (%)**	**Pyronaridine/Artesunate N=[355] n (%)**	**Artemether/Lumefantrine N=[180] n (%)**
Patients excluded from the EE population :	80 (22.5%)	41 (22.8%)	**NA**	**NA**
PCR-corrected ACPR on Day 42				
Available observations	275 (100%)	139 (100%)	255 (100%)	180 (100%)
Number of patients cured	257	133	262	135
Cure rate (%)	93.5	95.7	73.8	75.0
95% CI*	89.9; 96.1	90.8; 98.4	68.9; 78.3	68.0; 81.1
Between group comparison				
Difference	-2.2		-1.2	
95% CI**	-6.5; 1.3		-8.7; 6.9	
Conclusion from the applicant ***	Non-inferiority		Non-inferiority	
Rapporteur's opinion ****	***Non-inferiority not recognised***		***Non-inferiority not recognised***	
P-value*****	0.359		0.765	
Number of treatment failure	18 (6.5%)	6 (4.3%)	93 (26.2%)	45 (25.0%)
Early treatment failure	2 (0.7%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Late clinical failure	2 (0.7%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Late parasitological failure	14 (5.1%)	6 (4.3%)	14 (3.9%)	6 (3.3%)
Unknown (missing data) (a+b)	0 (0.0%)	0 (0.0%)	75 (21.1%)	39 (21.7%)
a) Previous New Infection	*0 (0.0%)*	*0 (0.0%)*	*51 (14.4%)*	*26 (14.4%)*
b) Other	*0 (0.0%)*	*0 (0.0%)*	*24 (6.8%)*	*13 (7.2%)*

ACPR = adequate clinical and. parasitological response, EE = efficacy evaluable, ITT = intent to treat,
PCR = polymerase chain reaction
Note: Percentages are based on available observations
Patients who discontinued treatment due to an adverse event were classified as Early Treatment Failures according to a medical review.
* Exact two-sided 95% Confidence Interval (Pearson-Clopper)
** The two-sided Confidence Interval for between group comparison was calculated using Newcombe-Wilson method
*** Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -10%
**** The rapporteurs consider that the -10 % non inferiority limit is too low (see comment further below in the text)
*****Two-sided Chi-square test for superiority (performed only when non-inferiority had been demonstrated)

Table 11: Day 42 Crude ACPR in the EE population and the ITT population-SP-C-007-07

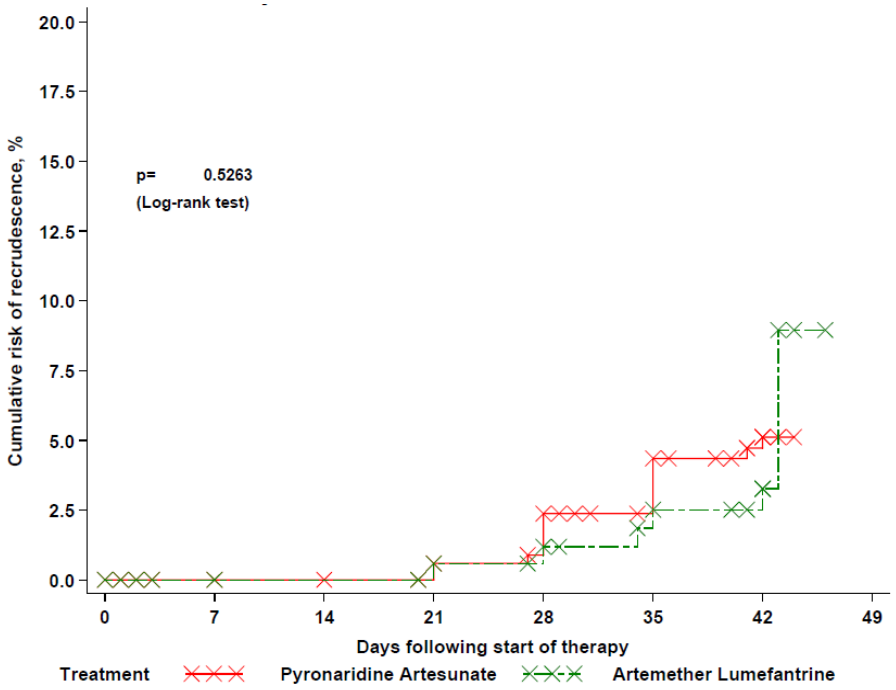
	EE population		**ITT population**	
	Pyronaridine/Artesunate N=[325] n (%)	**Artemether/Lumefantrine N=[166] n (%)**	**Pyronaridine/Artesunate N=[355] n (%)**	**Artemether/Lumefantrine N=[180] n (%)**
Patients excluded from the EE population :	30 (8.4%)	14 (7.8%)	**NA**	**NA**
Crude ACPR on Day 42				
Available observations	325 (100%)	166 (100%	355 (100%)	180 (100%)
Number of patients cured	249	130	254	132
Cure rate (%)	76.6	78.3	71.5	73.3
95% CI*	71.6; 81.1	71.3; 84.3	66.5; 76.2	66.2; 79.6
Between group comparison				
Difference	-1.7		-1.8	
95% CI**	-9.1; 6.4		-9.5; 6.4	
Conclusion from the applicant***	Non-inferiority		Non-inferiority	
Rapporteurs' opinion ****	***Non-inferiority not recognised***		***Non-inferiority not recognised***	
P-value*****	0.671		0.664	
Number of treatment failures	76 (23.4%)	36 (21.7%)	101 (28.5%)	48 (26.7%)
Early treatment failure	2 (0.6%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Late clinical failure	14 (4.3%)	5 (3.0%)	14 (3.9%)	5 (2.8%)
Late parasitological failure	60 (18.5%)	31 (18.7%)	61 (17.2%)	31 (17.2%)
Unknown (missing data) (a+b)	0 (0.0%)	0 (0.0%)	24 (6.8%)	12 (6.7%)
a) Previous New Infection	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*
b) Other	*0 (0.0%)*	*0 (0.0%)*	*23 (6.5%)*	*12 (6.7%)*

ACPR = adequate clinical and. parasitological response, EE = efficacy evaluable, ITT = intent to treat,
PCR = polymerase chain reaction
Note: Percentages are based on available observations
Patients who discontinued treatment due to an adverse event were classified as Early Treatment Failures according to a medical review.
* Exact two-sided 95% Confidence Interval (Pearson-Clopper)
** The two-sided Confidence Interval for between groups comparisons was calculated using Newcombe-Wilson method
*** Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -10%
**** The rapporteurs consider that the -10 % non inferiority limit is too low (see comment further below in the text)
***** Two-sided Chi-square test for superiority (performed only when non-inferiority had been demonstrated)

Ancillary analyses

Based on Kaplan-Meier estimates, the cumulative risk of recrudescences through Day 42 was not statistically significant different between PA and AL groups (p=0.5263), neither with regards to new infection (p=0.7740), nor parasite re-appearance (p=0.9800). However, there is a tendency of higher recrudescence rate at Day 42 in the AL.

Figure 10: Kaplan-Meier Estimates of Recrudescence Rate – ITT Population - SP-C-007-07



Note: p=0.5263 based on the log rank test of equality of survival curves between the treatment groups

Of note, in the subgroup analysis at Day 42, children under 5 years and patients in Asia appeared to have the lowest cure rate. Noticeable lower cure rates (termed PCR-corrected ACPR) appear in children less than 5 years (in EE and ITT population) as compared to older i.e. 5 to 12 years age population.

The results in Asia were lower as compared to Africa countries in the ITT population (69.2% vs. 100% respectively) but as the sample size is small, power is limited.

In summary, in this study SP-C-007-07, the applicant has chosen a non inferiority margin of -10% instead of -5% (as was employed in the other studies). However, this non inferiority limit is considered too low, in view of the high efficacy expected and cure rates appear very low (< 90%) in the PA group with treatment failures/recrudescences consistently higher in the PA group as compared to the AL group.

Parasite clearance time:

Pyronaridine tetraphosphate/artesunate and AL were rapidly effective on parasitaemia. Parasite count decreased rapidly (during the first 16 hours) similarly in both the PA and AL groups.

Based on Kaplan-Meier estimates, time to parasite clearance was marginally statistically significantly (p=0.0459) shorter in the PA group compared with the AL group. In the EE population, a slightly higher percentage of PA vs. AL subjects achieved parasite clearance 24 hours after the first dose (49.9% vs. 43.7%). At 48 hours after first dosing 95.5 % and 95.2 % had achieved parasite clearance in the PA and AL group respectively, and at 72 hours after first dose results were 97.0 % vs. 98.8 % in PA and AL respectively. Median time to parasite clearance was 24.1 and 24.2 hours in the PA and AL groups, respectively.

Time to fever clearance was similar in the PA and AL groups. Most of patients took antipyretics.

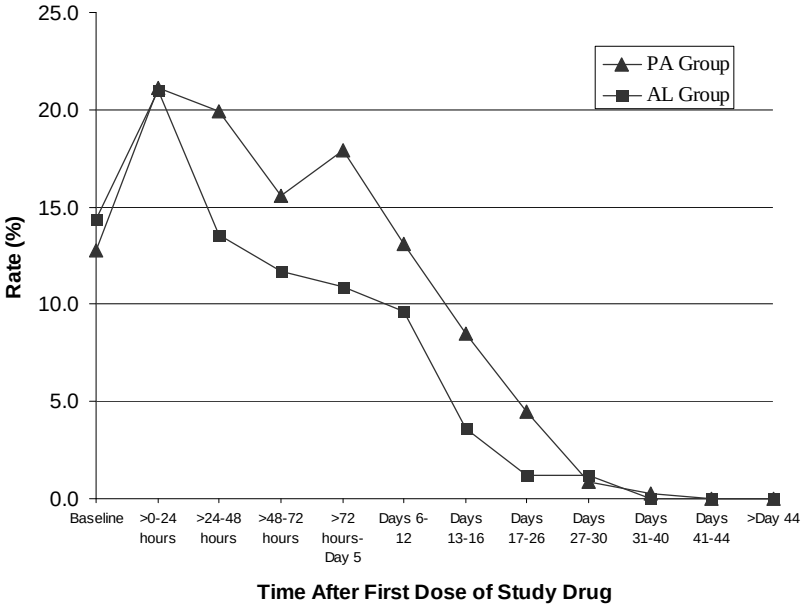
Subjects weighing 24 kg to 25 kg:

In this study, a difference in Day 28 PCR-corrected ACPR was observed by study drug dose as subjects who received PP >11 mg/kg had higher PCR-corrected ACPR than those who received ≤ 8.5 mg/kg (100.0% vs. 94.6%). Also, according to the integrated population pharmacokinetic analysis that is provided by the applicant, the amount of pyronaridine given to subjects in the treatment failure group was ≤ 8.5 mg/kg in 20 of the 50 paediatric subjects. The applicant suggests an adjustment to increase the recommended dose with tablets for patients 24 kg to 25 kg body weight from one tablet to 2 tablets (as proposed in the SPC). As such, the dose recommended by the applicant in patient weighing 24 kg increases from 7.5 mg/kg to 15 mg/kg and from 7.2 mg/kg to 14.4 mg/kg in patients weighing 25 kg with respect to pyronaridine. For AS, this corresponds to an increase from 2.5 mg/kg to 5 mg/kg in patients weighing 24 kg and from 2.4 mg/kg to 4.8 mg/kg in patients weighing 25 kg (i.e. 2 tablets instead of 1 tablet as proposed in the SmPC). This proposed regimen corresponds to the higher limit of the dose ranges administered in the phase III tablets clinical studies. Although any extrapolation from this study must remain cautious as granules formulation were used and a limited sample of children weighing 24 kg to 25 kg have been included in the tablets formulation clinical study, this adjustment of posology for tablet formulation can be accepted within the margin of available data, especially considering that children have low immunity and are prone to severe malaria progression.

Gametocytes:

The percentage of subjects with gametocytes was low at Day 0, hour 0 (ITT population: PA: 44 patients =12.4%; AL: 26 patients =14.4%;), rose through Hour 48, and gradually decreased to zero over time in both groups at Day 42. At Day 17-26, 15 patients had gametocytes in the PA group and 2 in the AL group (EE population). The time to clearance over the 3 days of treatment was not significantly different between the groups but when comparing the rate of gametocytes over the 42 days of the study, the carriage of gametocytes appears longer in the PA group than in the AL group.

Figure 11: Percentage of Subjects With Gametocytes Over Time – EE Population- SP-C-007-07



- ***Plasmodium vivax*:**

Study SP-C-006-06: "A Phase III Multi-Centre, Randomised, Double-Blind, Double-Dummy, Comparative Clinical Study to Assess the Safety and Efficacy of a Fixed-Dose Formulation of Oral Pyronaridine/Artesunate (180:60 mg Tablet) Versus Chloroquine (155 mg Tablet), in Children and Adult Patients With Acute *Plasmodium vivax* Malaria"

Methods

This was a multi-centre, controlled, randomised, double blinded, double dummy, 2 parallel groups, non-inferiority phase III clinical trial conducted at 5 sites in Asia (Cambodia, India, Indonesia, Thaïland (2)).

Study Participants

Male or female subjects with body weight between 20 and 90 kg (and no evidence of severe malnutrition), between the ages of 3 and 60 years, inclusive, and with acute uncomplicated *Plasmodium vivax* mono-infection confirmed by fever (axillary/tympanic temperature ≥ 37.5°C or oral/rectal temperature ≥ 38°C, or documented history of fever in the previous 24 hours) and positive microscopy of *P. vivax* with parasite density ≥ 250µl of blood (including at least 50 % of asexual parasites) were eligible for enrolment.

Exclusion criteria were as follows:

1. Presence of a mixed *Plasmodium* infection.
2. Presence of other clinical condition requiring hospitalisation.
3. Presence of significant anaemia, as defined by haemoglobin <8 g/dL.
4. Known history or evidence of clinically significant disorders, such as cardiovascular (including arrhythmia, QTc interval ≥450 milliseconds); respiratory (including active tuberculosis); history of jaundice, hepatic, renal, gastrointestinal, immunological (including active human immunodeficiency virus [HIV]-acquired immune deficiency syndrome), neurological (including auditory), endocrine, infectious, malignancy, psychiatric, or other abnormality (including recent head trauma).
5. Known history of hypersensitivity, allergic or adverse reactions to pyronaridine, chloroquine, or AS or other artemisinins.
6. Known history of hypersensitivity, allergic, or adverse reactions to chloroquine, primaquine, and related agents.
7. Known active Hepatitis A IgM, Hepatitis B surface antigen or Hepatitis C antibody.
8. Known seropositive HIV antibody.
9. Receipt of any anti-malarial treatment in the preceding 2 weeks, as determined by history and, whenever feasible, by screening test.
10. Receipt of antibacterial with known anti-malarial activity in the preceding 2 weeks.
11. Receipt of any investigational drug within the past 4 weeks.
12. Liver function tests (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) >2.5 x upper limit of normal (ULN).
13. Known significant renal impairment, as indicated by serum creatinine level >1.4 mg/dL.

14. Female subjects of child-bearing potential were to be neither pregnant (as demonstrated by a negative pregnancy test) nor lactating, and were to be willing to take measures to not become pregnant during the study period.

15. Previous participation in the present clinical study with PA.

Treatments

Subjects received either oral PA (180:60-mg tablets) plus chloroquine-placebo once a day for 3 consecutive days (days 0, 1, and 2) or chloroquine (155-mg tablets) plus PA-placebo once a day for 3 consecutive days (days 0, 1 and 2).

PA dose and schedule:

The daily dose of PA was dependent on the subject's body weight; subjects received between 7.2:2.4 mg/kg and 13.8:4.6 mg/kg. Dose was depending on body weight:

- 20-25 kg, 1 tablet
- 26-44 kg, 2 tablets
- 45-64 kg, 3 tablets
- 65-90 kg, 4 tablets

Chloroquine dose and schedule

The daily dose of chloroquine was 620 mg on Days 0 and 1 and 310 mg on Day 2 for adults and 10 mg/kg chloroquine base on Days 0 and 1 and 5 mg/kg on Day 2 for children. The dosage in children was not to exceed the adult dose regardless of weight.

Table 12: Children Chloroquine Dosing Regimen

Subject's Weight (kg)	Number of Tablets Days 0 and 1	Number of Tablets Day 2
20-23	1	0.5
24-27	1.5	1
28-38	2	1
39-40	3	1.5

Primaquine dose and schedule

The daily dose of primaquine base was 15 mg for adults and 0.3 mg/kg for children. Adults dosed with primaquine received 1 tablet (15 mg) a day on days 28 through 42. Children 20-35 kg received 0.5 tablet per day on days 28-42 and children >35 kg received 1 tablet per day on days 28-42

Study drug and comparator drugs were given to each subject by a qualified member of the study site who was designated by the investigator with up to 240 mL (full glass) water. All parties remained blind to treatment assignment. All tablets were to be swallowed whole. Subjects were to take the medication in an upright position (seated or standing); food may have been given prior to study drug administration.

Objectives

The main objectives of this clinical study were to compare the efficacy and safety of the fixed combination of pyronaridine: artesunate combination (180:60 mg tablets) PA with that of chloroquine

(Malachlo® tablets supplied by Shin Poong) in children and adults with acute, uncomplicated *P. vivax* malaria.

Outcomes/endpoints

The **primary efficacy endpoint** for the study SP C-006-06 was the cure rate on Day 14.

The efficacy endpoint "crude cure rate" was defined as no parasitaemia irrespective of axiliary temperature" is in agreement with the WHO protocol. Genotyping by PCR was used as an exploratory tool to differentiate re-infection (new infection) from recrudescence or relapse (relapse being parasitaemia originating from latent hypnozoites). Although a common technical protocol was used for PCR sampling and analysis, the evaluation of PCR-corrected cure rate was an exploratory end point because the tests used to perform the analysis to date are not fully validated. In contrast to *Plasmodium falciparum,* PCR is not useful at present to differentiate between recrudescence and relapse, and the Evaluable Efficacy population was defined as the population with available observation at Day 14.

Patients who discontinued the study prior to Day 14 without being treatment failure (crude cure rate) were excluded from the EE population due to missing primary end point data; those were classified as failure in the ITT population.

Note

At the time that the studies were conducted Day 14 was considered to be appropriate according to WHO protocol in use at that time. It is remarked that the choice of Day 14 measurement as primary endpoint is controversial; Day 28 is now considered more rational and is in line with the latest version of the WHO protocol. Day 42 is probably less appropriate, though as primaquine has little effect on blood trophozoïtes, this date for assessment can also be considered.

The **secondary efficacy endpoints** were:

- Cure rate on Day 21 and Day 28, defined in the same way as cure rate on Day 14.
- Parasite Clearance Time (PCT): defined as the time from first dosing to time of first blood draw with parasite clearance. Parasite clearance was defined as zero presence of asexual parasites for two consecutive negative readings taken between 8 and 24 hours apart.
- Fever Clearance Time (FCT): defined as the time from first dosing to first normal reading of temperature (<37.5 °C taken axillary or tympanic) for two consecutive normal temperature readings taken between 8 and 24 hours apart. The method of temperature measurement must be the same (i.e. axillary, tympanic, oral or rectal) for all measures in the same patient. Those patients who are initially included on history of fever and who did not subsequently have a documented temperature reading of over 37.5 °C (taken axillary or tympanic) during the 24 hours following initial dosing, were included in this endpoint analysis.
- Proportion of patients who had cleared parasites on Day 1, 2 and 3
- Proportion of patients who had cleared fever on Day 1, 2 and 3

Treatment failure is defined as any of the following:

- Clinical deterioration due to *P. vivax* illness requiring hospitalisation in the presence of parasitaemia until Day 14.
- Presence of *P. vivax* parasitaemia and axillary temperature ≥37.5°C at any time between day 3 and 14.

- Presence of *P. vivax* parasitaemia on any day between day 7 and 14, irrespective of the clinical condition.

Safety endpoints:

- Incidence of any adverse events or clinically significant laboratory abnormalities
- Vital signs, new physical examination abnormalities
- ECG abnormalities

Exploratory Endpoints:

- Proportion of patients with PCR-corrected cure on Day 14
- Proportion of patients with PCR-corrected cure on Day 28
- Cure rate on Day 42
- Proportion of patients with PCR-corrected cure on Day 42
- Genotyping of *P. falciparum*-specific polymorphic genes by PCR is well established to distinguish recrudescence from new infection. However, in the case of *P. vivax*, polymorphic molecular markers have not been fully validated. Current molecular tools may identify new infection (or relapse from a previous infection) but cannot distinguish relapse (of current infection) from recrudescence. Endpoints determined by PCR analysis will be regarded as exploratory. New infection as evidenced by PCR-genotyping studies will be considered as treatment success.

Sample size

The sample size was estimated assuming a cure rate on Day 14 of 90% in both treatment groups and assuming a non-inferiority limit of -10%, then a sample size of 410 evaluable subjects randomised in a 1:1 ratio (205 subjects in each treatment group) would provide 90% power to demonstrate non-inferiority of PA compared to chloroquine, using a 2-sided 95% CI with normal approximation. Assuming a dropout rate of 10%, 456 subjects would be randomised to the study (228 subjects in each treatment group).

Assuming a cure rate on Day 14 of 95%, this sample size would provide >99% power to demonstrate non-inferiority of PA compared to chloroquine.

Sample size estimation was performed using nQuery statistical software i.e. Newcombe-Wilson score method.

Randomisation

Subjects who met all entry criteria and no exclusion criteria were randomised in a 1:1 ratio to receive either PA (plus matching placebo of chloroquine) or chloroquine (plus matching placebo of PA) according to the randomisation scheme provided by the Sponsor or designee. The randomisation scheme was generated using permutation blocks technique. Complete blocks were assigned to each study site. Subjects were assigned, in ascending order, a randomisation number according to the order recruited. The subject was allocated an individually numbered treatment pack, which contained sufficient tablets for 3 days' therapy plus an overage bottle containing tablets in case the subject vomited the first dose. Subjects were allocated the following identification nomenclature according to the order recruited within any given site: site code - subject number.

Blinding (masking)

In order to minimise subject selection bias, study drug was administered to subjects by a qualified member of the study site who was designated by the Investigator. All parties were blind to treatment assignment and were not informed of treatment allocation unless the blind needed to be broken for a medical emergency. Sealed envelopes containing the study medication assignment for each subject were provided to the Investigator. The envelopes were retained by the Investigator (or designee) in a secure area and were to be opened in case of emergency only if the Investigator(s) needed to know the study medication in order to manage the subject's condition. The Sponsor was to be notified before breaking the blind, unless identification of the study medication was required for emergency therapeutic measures. The Sponsor was then to be notified within 24 hours of the blind being broken. The date that the blind was broken, the reason for the unblinding, and the name of the person performing the unblinding were to be recorded in the source documents and on the CRF. All code break envelopes (opened and unopened) were to be returned to the Sponsor at the end of the study. However, no code breaks were required.

Statistical methods

The EE analysis was considered the primary efficacy analysis. Efficacy analysis was performed on both the EE and ITT populations. The analysis was also performed in the Exploratory EE population redefined per amendment to the SAP when some discrepancies were found during PCR analysis in the determination of species between the PCR analysis done by STI and the slide reading at the sites of different origin.

A 2-sided 95% confidence interval (CI) (corresponding to a 1-sided 97.5% CI) for the difference in the 2 treatment groups in Day 14 cure rates was calculated in the EE population. The non-inferiority margin was -10%. Non-inferiority was claimed if the lower limit of the 2-sided 95% CI for the difference in cure rates on Day 14 was not lower than -10%. The CI was calculated according to the Newcombe-Wilson method without continuity correction. Furthermore, exact (Pearson-Clopper) 95% CIs were calculated for the Day 14 cure rate in each of the 2 treatment groups.

The primary efficacy analysis performed on Day 14 was repeated for the proportion of subjects with cure on Days 21 and 28. The parasitological clearance time (PCT) and fever clearance time (FCT) were summarised using Kaplan-Meier estimates. Treatment group comparison of PCT and FCT were done by means of the log-rank test. Subjects who did not have confirmed PCT or FCT within 72 hours after the first treatment intake were censored at that time point.

The proportion of subjects who had parasite clearance and/or fever clearance on Day 1 (24 hours after first dose), Day 2 (48 hours after first dose), and Day 3 (72 hours after first dose) were calculated using Kaplan-Meier estimates. The associated 95% CIs were also calculated.

Results

Participant flow

A total of 456 subjects aged from 7 to 60 years were randomised in a 1:1 ratio (n=228, n=228) to receive for 3 consecutive days, either oral pyronaridine/artesunate (PA) (180:60mg tablets) once a day (PP: 6.9 to 13.8 mg/kg/dose; AS: 2.4 to 4.6 mg/kg/dose) or oral chloroquine 25 mg/kg as 10 mg/kg once a day for 2 days and 5 mg/kg once a day the third day.

The majority of subjects completed the 3 days treatment: 97.8%=446/456 (PA group: 99.1% = 226/228; chloroquine group: 96.5% = 220/228) and 83.3% = 380/456 completed the study (PA

group: 84.6% (193/228); chloroquine: 82%= 187/228). In other words, 2.2% (10/456 patients) discontinued the 3 treatment and overall 16.7% (76/456 patients) discontinued the study. A greater percentage of chloroquine subjects than PA subjects prematurely discontinued (chloroquine: 18% as PA group 15.4%., primarily due to infection with *P. falciparum* malaria (6.1% vs. 2.2%).

Table 13 Subject Disposition – All Randomised Subjects

	PA n (%)	Chloroquine n (%)	Total n (%)
Subjects randomised	228 (100.0)	228 (100.0)	456 (100.0)
Subjects randomised but not treated	0	0	0
Subjects treated[a]	228 (100.0)	228 (100.0)	456 (100.0)
Subjects who completed treatment[b]	226 (99.1)	220 (96.5)	446 (97.8)
Subjects who completed study	193 (84.6)	187 (82.0)	380 (83.3)
Withdrawn from study prematurely	35 (15.4)	41 (18.0)	76 (16.7)
Adverse event/SAE	0 (0.0)	2 (0.9)	2 (0.4)
Consent withdrawn	2 (0.9)	5 (2.2)	7 (1.5)
Lost to follow-up	19 (8.3)	12 (5.3)	31 (6.8)
Protocol violation/non-compliance	1 (0.4)	0 (0.0)	1 (0.2)
Other	13 (5.7)	22 (9.6)	35 (7.7)
Re-appearance of *P. vivax*/treatment failure	6 (2.6)	7 (3.1)	13 (2.9)
Subject missed visit	1 (0.4)	0 (0.0)	1 (0.2)
Mixed infection at entry	1 (0.4)	0 (0.0)	1 (0.2)
P. falciparum malaria	5 (2.2)	14 (6.1)[c]	19 (4.2)
Subject left hospital without informing staff	0 (0.0)	1 (0.4)	1 (0.2)

Note: Percentages are based on the number of randomised subjects.
a. Received ≥1 dose of study medication.
b. Received all 3 planned doses of study medication.
c. Includes 1 subject with *P. falciparum* found in a pre-dose slide.
Cross Reference: Statistical Table 14.1.1 and Appendices 16.2.1.1, 16.2.1.2, and 16.2.6.4.

Recruitment

The study report states that first patient enrolled on 10 March 2007 and last patient completed on 31 March 2008.

Baseline data

Overall, 33.8% of subject participated at a site in Cambodia (Pailin): 33.8%, 17.5% at a site in India (Mangaladore), 5.3% at a site in Indonesia (Maumere), and 43.4% at 2 sites in Thailand (Mae Sot, Mae Ramat). At the time the trial was implemented, in general, there were no issues with chloroquine resistance in the areas where the trial was conducted (ethics reasons).

Most subjects were male (73.7%); mean age was 26.7 years ranging from 7 to 60 years with only 13 children (5.9%) less than 12 years in the PA group (11 in the chloroquine group). Body weight ranged between 20 kg to 80 kg.

Antimalarial co-medication during the study was a reason for exclusion during the study or classification as treatment failure. According to the inclusion criteria, asymptomatic patients were not to be included and acute uncomplicated *P. vivax* infections had to be confirmed by the presence of fever (either measured or documented during the 24 hours before inclusion) and positive microscopy (parasite density ≥ 250/mcL). At baseline, approximately 47% of patients had fever recorded and 54% had a history of fever.

Numbers analysed

The number of subjects in each analysis population is presented in the table below

Table 14: Number (%) of Subjects in Analysis Populations – All Randomised Subjects

Population	PA n (%)	Chloroquine n (%)	Total n (%)
Intent-to-treat (ITT)	228 (100.0)	228 (100.0)	456 (100.0)
Efficacy evaluable (EE)	218 (95.6)	209 (91.7)	427 (93.6)
Exploratory EE	216 (94.7)	200 (87.7)	416 (91.2)
Safety	228 (100.0)	228 (100.0)	456 (100.0)

Note: Percentages are based on the number of randomised subjects.
Cross Reference: Statistical Table 14.1.3 and Appendix 16.2.3.1.

The EE (efficacy evaluable) population on Day 14 included 427 (93.6%) patients (PA: 218/228= 95.6%; chloroquine: 209/228 = 91.7%) as 6.4 % were excluded from the EE analysis in a greater rate in the chloroquine group: 8.3% excluded (19 patients/228) vs. PA: 4.4% excluded (10 patients/228). After Day 14 the exclusion rate from EE population was similar in both groups: 8.3% (=19/228) leading to 418 patients analysed in the EE population.

Outcomes and estimation

See also Tabular Summary – Table 17

In the EE population, all patients were counted as cured on Day 14 (defined as absence of *P. vivax* parasitaemia, irrespective of body temperature, without previously meeting any of the criteria of treatment failure) except one patient in the PA group. This patient appears as Indonesian-Maumere female patient aged more than 12 years with previous history of malaria in the last 12 years.

In the ITT population, the crude cure rates were PA: 95.2% = 217/228 [IC95%: 91.5, 97.6] vs. chloroquine 93.0%= 212/228 [IC95%: 88.9%, 95.9%]. Non inferiority was concluded as the 95% CI of the between group difference (PA minus chloroquine) was: = 2.2 [IC95%: -2.3%, 6.8%].

At day 28 (primary endpoint according the WHO protocol) cure rate was 88.6% in the PA group compared to 85.5% in the CQ group (ITT analysis) and 97.1% vs. 98% respectively for the EE analysis. The greatest difference between the PA and chloroquine groups was observed for crude cure rate on Day 42 (95.5% vs. 92.1%, respectively in the EE population; and 83.3 % vs. 78.1 % in respectively in the ITT population.

A total of 76 patients (16.6%) i.e. PA: 15.4% (35/228) and chloroquine 18.0% (41/228). were discontinued during the study.

Re-appearance of *Plasmodium vivax* was observed in 13 cases (PA: 6 patients, Chloroquine: 7).

Ancillary analyses

In the subgroup analysis based on sites, non-inferiority was not demonstrated at Day 14, 28, 42 in India and Indonesia (Maumere) and in Cambodia at Day 28 as compared to chloroquine in the ITT population.

As the number of patients at that site was very small, no reliable conclusion can be drawn. Pyronaridine/artesunate and chloroquine were both rapidly effective on parasitemia. *P. vivax* parasite count decreased rapidly (during the first 16 hours) in both the PA and chloroquine groups. Time to parasite clearance was statistically significantly ($p<0.0001$) shorter in the PA group compared with the chloroquine group. A greater percentage of PA subjects vs. chloroquine subjects achieved parasite clearance 24 hours (71.6% vs. 30.6%) and 48 hours (99.5% vs. 88.0%) after the first dose. After 72 hours following the first dose, all patients in the PA group and 97% of patients in the CQ group had achieve complete parasite clearance. Times to parasite clearance (medians: 23.1 vs. 32.0 hours) and fever clearance (medians: 15.8 vs. 23.8 hours) were statistically significantly ($p<0.0001$ and $p=0.0071$, respectively) shorter in the PA group than the chloroquine group. As around 80% of the patients received antipyretic treatment during the first day, no reliable conclusion can be drawn on fever clearance time.

~~P~~ost hoc analysis showed a statistically lower risk of infection with *P. falciparum* ($p=0.0481$) with PA than with chloroquine, based on parasitology data. The lower risk of infection with PA compared with chloroquine may be due to the increased resistance of *P. falciparum* to chloroquine.

Overall the cure rates in both the efficacy evaluable (EE) and intention to treat (ITT) cohorts from this study would support the relative efficacy of PA over CQ in adults but, in children, only 14 and 13 children less than 12 years were included in PA and CQ groups respectively.

Gametocytes:

In this study gametocytes were observed at baseline in 373 subjects (PA: 192; chloroquine: 181) but were not recorded during the study, since it was regarded as having limited value with respect to the *P. vivax* sexual cycle. Even though the microscopic count of gametocytes is not expected to have added additional difficulties or expenses, it can be agreed that there are inherent differences between the *P. falciparum* and the *P. vivax* parasite life cycle as mature and infective gametocytes of *P. vivax* appear in the blood of an infected person almost simultaneously with the asexual blood stage parasites and before the clinical threshold of a blood infection is reached. Therefore, gametocytes will be transmitted to mosquitoes mostly before the beginning of the clinical symptoms and before the patient receives treatment. However, bearing in mind the observations of longer *P. falciparum* gametocytes carriage in patients treated with Pyramax, the issue may also pertain to *P. vivax* and the applicant is requested to further address this issue in the future paediatric *P. vivax* study that is planned in Papua New Guinea (Study SP-C-011-10).

Study SP-C-008-07: "A Phase III, Randomised, Double-Blind, Double-Dummy, Comparative Clinical Study to Assess the Safety and Efficacy of a Fixed-Dose Formulation of Oral Pyronaridine/Artesunate (180:60 mg Tablet) Versus Chloroquine, in Children and Adult Patients in Korea with acute *Plasmodium vivax* malaria"

SP-C-008-07 study report (dated on September 2011) was submitted by the applicant in October 2011. The study began on 6th September 2007 and due to slow recruitment, the study was terminated prematurely by the sponsor (November 2010) after 30 subjects had been included instead of 40 patients that were initially planned.

This study was conducted in Korea (Seoul, Goyang-si). It was a randomised, double blinded, double dummy, comparative clinical trial comparing fixed-dose formulation of oral pyronaridine:artesunate (180:60 mg tablet) versus chloroquine for 3 days in patients (children and adults) with uncomplicated *Plasmodium vivax.*

The objectives and design of this study were similar to SP-C-006-06 and the applicant anticipated to pool the results of the 2 studies.

A total of 30 adults aged from 17 to 58 years were randomised in a 1:1 ratio (n=15, n=15) to receive for 3 consecutive days, either oral pyronaridine/artesunate (PA) (180:60mg tablets) once a day (PP: 6.9 to 13.8 mg/kg/dose; AS: 2.4 to 4.6 mg/kg/dose) or oral chloroquine 25 mg/kg for 3 days as 10 mg/kg once a day for 2 days and 5 mg/kg once a day the third day.

The ITT population consisted of 29 subjects (PA: 14; CQ: 15) and 28 adults (PA/ 13; CQ: 15) were analysed in the EE population. All 28 patients were cured at Day 14 and the crude cure rate was 100 % at Day 28 and at Day 42 in both treatment groups as no re-appearance of parasites occurred.

Time to parasite clearance was statistically shorter in the PA group compared with chloroquine group. Median time to parasite clearance was 32.0 and 63.9 hours in the PA and chloroquine groups, respectively.

The applicant provided the pooled analysis of the two *Plasmodium vivax* studies but this was not of much value as study SP-C-008-07 was very small numerically (and no children) and the pooling data add little to the overall effect size.

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 15: Summary of Efficacy for trial SP-C-004-06

Title: A Phase III Comparative, Open-label, Randomised, Multi-Centre, Clinical Study to Assess the Safety and Efficacy of fixed dose formulation oral pyronaridine artesunate (180:60mg tablet) versus mefloquine (250 mg tablet) plus artesunate (100 mg tablet) in children and adult patients with acute uncomplicated *Plasmodium falciparum* malaria			
Study identifier	SP-C-004-06		
Design	multicentre, comparative, randomised, open-label, parallel group, non-inferiority study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		42 days not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	PA		Pyronaridine/Artesunate, 3 days, 848
	MQ + AS		Mefloquine + Artesunate, 3 days, 423
Endpoints and definitions	Primary endpoint	COR-EE-D28	Day 28 PCR-corrected ACPR in EE population
	Secondary endpoints	S1: COR-ITT-D28	Day 28 PCR-corrected ACPR in ITT population
		S2: COR-<POP>-<DAY>	PCR-corrected ACPR at days 14 and 42 in EE and ITT populations
		S3: CRU-<POP>-<DAY>	Crude cure rate at days 14, 28 and 42 in EE and ITT populations
		S4	Proportion of aparasitaemic patients and time to parasite clearance
		S5	Proportion of afebrile patients and time to fever clearance
		S6	Proportion of patients with gametocytes by time points
Database lock	12 January 2009		

Results and Analysis

Analysis description	**Primary Analysis: COR-EE-D28**		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	749	368
	COR-EE-D28 (N (%))	743 (99.2%)	360 (97.8%)
Effect estimate per comparison	Primary endpoint	Comparison groups	PA – MQ + AS
		Difference	1.4
		95% two-sided CI	0.0 ; 3.5
		p-value	0.053
Notes	CI = Confidence Interval		

Analysis description	**Secondary analysis S1: COR-ITT-D28**		
Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	848	423
	COR-ITT-D28 (N (%))	793 (93.5%)	387 (91.5%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	2.0
		95% two-sided CI	-0.9 ; 5.4
		p-value	0.187
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S2: COR-EE-D14, COR-EE-D42 COR-ITT-D14, COR-ITT-D42**		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	765	375
	COR-EE-D14 (N (%))	764 (99.9%)	372 (99.2%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	0.7
		95% two-sided CI	-0.1 ; 2.2
		p-value	0.073
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	698	339
	COR-EE-D42 (N (%))	661 (94.7%)	329 (97.1%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	-2.4
		95% two-sided CI	-4.7 ; 0.4
		p-value	0.088
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 14		

Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	848	423
	COR-ITT-D14 (N (%))	815 (96.1%)	401 (94.8%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	1.3
		95% two-sided CI	-1.0 ; 4.1
		p-value	0.280
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	848	423
	COR-ITT-D42 (N (%))	705 (83.1%)	355 (83.9%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	-0.8
		95% two-sided CI	-4.9 ; 3.7
		p-value	0.722
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S3: CRU-EE-D14, CRU-EE-D28, CRU-EE-D42 CRU-ITT-D14, CRU-ITT-D28, CRU-ITT-D42**		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	765	375
	CRU-EE-D14 (N (%))	764 (99.9%)	372 (99.2%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	0.7
		95% two-sided CI	-0.1 ; 2.2
		p-value	0.073
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	750	370
	CRU-EE-D28 (N (%))	739 (98.5%)	355 (95.9%)

Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	2.6
		95% two-sided CI	0.6 ; 5.2
		p-value	0.007
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	721	355
	CRU-EE-D42 (N (%))	662 (91.8%)	325 (91.5%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	0.3
		95% two-sided CI	-3.1 ; 4.1
		p-value	0.881
Analysis population and time point description	ITT population Day 14		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	848	423
	CRU-ITT-D14 (N (%))	815 (96.1%)	400 (94.6%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	1.5
		95% two-sided CI	-0.8 ; 4.4
		p-value	0.206
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	848	423
	CRU-ITT-D28 (N (%))	789 (93.0%)	382 (90.3%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	2.7
		95% two-sided CI	-0.4 ; 6.3
		p-value	0.088
Notes	CI = Confidence Interval		

Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	MQ + AS
	Number of subjects	848	423
	CRU-ITT-D42 (N (%))	708 (83.5%)	351 (83.0%)
Effect estimate per comparison		Comparison groups	PA – MQ + AS
		Difference	0.5
		95% two-sided CI	-3.7 ; 5.0
		p-value	0.818
Analysis description	**Secondary analysis S4: Proportion of aparasitaemic patients and time to parasite clearance**		
Analysis population and time point description	ITT population		
Kaplan-Meier estimate	Treatment group	PA	MQ + AS
	Number of subjects	848	423
	Aparasitaemic at Day 1 (% (95% CI))	37.1 (34.0 ; 40.5)	29.3 (25.2 ; 33.9)
	Aparasitaemic at Day 2 (% (95% CI))	81.0 (78.3 ; 83.6)	76.4 (72.2 ; 80.3)
	Aparasitaemic at Day 3 (% (95% CI))	92.2 (90.3 ; 93.9)	92.0 (89.1 ; 94.3)
	Median time to parasite clearance (hours (95% CI))	31.8 (31.6 ; 31.9)	32.1 (31.9 ; 39.1)
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S5: Proportion of afebrile patients and time to fever clearance**		
Analysis population and time point description	ITT population		
Kaplan-Meier estimate	Treatment group	PA	MQ + AS
	Available observations	712	356
	Afebrile at Day 1 (% (95% CI))	77.0 (73.8 ; 80.0)	75.8 (71.3 ; 80.2)
	Afebrile at Day 2 (% (95% CI))	94.9 (93.2 ; 96.4)	94.4 (91.7 ; 96.4)
	Afebrile at Day 3 (% (95% CI))	98.7 (97.7 ; 99.4)	97.8 (95.8 ; 98.9)
	Median time to fever clearance (hours (95% CI))	16.0 (15.8 ; 16.0)	16.0 (15.8 ; 16.0)
Notes	CI = Confidence Interval Available observations = Subjects in the ITT population with fever at baseline		

Analysis description	**Secondary analysis S6:** **Proportion of patients with gametocytes by time points**		
Analysis population and time point description	ITT population		
Descriptive statistics Number of subjects with gametocytes (N (%))	Treatment group	PA	MQ + AS
	Number of subjects	848	423
	Screening	74 (8.7%)	51 (12.1%)
	Day 0 / H0	81 (9.6%)	49 (11.6%)
	Day 0 / H8	76 (9.0%)	46 (10.9%)
	Day 0 / H16	94 (11.1%)	45 (10.6%)
	Day 1 / H24	110 (13.0%)	46 (11.0%)
	Day 1 / H32	111 (14.0%)	49 (12.3%)
	Day 1 / H40	106 (14.6%)	46 (12.7%)
	Day 2 / H48	95 (15.7%)	40 (12.5%)
	Day 2 / H56	82 (14.9%)	33 (11.7%)
	Day 2 / H64	74 (14.3%)	29 (10.9%)
	Day 3	105 (12.5%)	38 (9.2%)
	Day 7	73 (8.9%)	21 (5.1%)
	Day 14	52 (6.5%)	10 (2.5%)
	Day 21	24 (3.0%)	2 (0.5%)
	Day 28	12 (1.5%)	0
	Day 35	1 (0.1%)	0
	Day 42	0	1 (0.3%)
Analysis population and time point description	Efficacy Evaluable population		
Descriptive statistics Number of subjects with gametocytes (N (%))	Treatment group	PA	MQ + AS
	Number of subjects	749	367
	Screening	63 (8.4%)	34 (9.3%)
	Day 0 / H0	70 (9.3%)	31 (8.4%)
	Day 0 / H8	64 (8.6%)	29 (7.9%)
	Day 0 / H16	78 (10.4%)	28 (7.6%)
	Day 1 / H24	92 (12.3%)	30 (8.2%)
	Day 1 / H32	91 (12.9%)	33 (9.5%)
	Day 1 / H40	88 (13.7%)	31 (9.9%)
	Day 2 / H48	79 (15.0%)	28 (10.3%)
	Day 2 / H56	71 (14.8%)	25 (10.2%)
	Day 2 / H64	66 (14.7%)	22 (9.5%)
	Day 3	88 (11.8%)	26 (7.1%)
	Day 7	60 (8.1%)	15 (4.1%)
	Day 14	44 (6.0%)	8 (2.2%)
	Day 21	19 (2.6%)	1 (0.3%)
	Day 28	11 (1.5%)	0
	Day 35	1 (0.1%)	0
	Day 42	0	1 (0.3%)

Table 16: Summary of Efficacy for trial SP-C-005-06

Title: A Phase III Comparative, (double-blind, double-dummy), randomised, multi-centre, clinical study to assess the safety and efficacy of fixed dose formulation of oral pyronaridine artesunate tablet (180:60 mg) versus Coartem (artemether lumefantrine) in children and adult patients with acute uncomplicated *Plasmodium falciparum* malaria			
Study identifier	SP-C-005-06		
Design	multicentre, comparative, randomised, (double-blind, double-dummy), parallel group, non-inferiority study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	42 days not applicable not applicable	
Hypothesis	Non-inferiority		
Treatments groups	PA		Pyronaridine/Artesunate, 3 days, 849
	AL		Artemether/Lumefantrine, 3 days, 423
Endpoints and definitions	Primary endpoint	COR-EE-D28	Day 28 PCR-corrected ACPR in EE population
	Secondary endpoints	S1: COR-ITT-D28	Day 28 PCR-corrected ACPR in EE population
		S2: COR-<POP>-<DAY>	PCR-corrected ACPR at days 14 and 42 in EE and ITT populations
		S3: CRU-<POP>-<DAY>	Crude cure rate at days 14, 28 and 42 in EE and ITT populations
		S4	Proportion of aparasitaemic patients and time to parasite clearance
		S5	Proportion of afebrile patients and time to fever clearance
		S6	Proportion of patients with gametocytes by time points
Database lock	29 July 2008		

Results and Analysis

Analysis description	**Primary Analysis: COR-EE-D28**		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	792	388
	COR-EE-D28 (N (%))	780 (98.5%)	384 (99.0%)
Effect estimate per comparison	Primary endpoint	Comparison groups	PA – AL
		Difference	-0.5
		95% two-sided CI	-1.8 ; 1.2
		p-value	0.499
Notes	CI = Confidence Interval		

Analysis description	**Secondary analysis S1: COR-ITT-D28**		
Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	849	423
	COR-ITT-D28 (N (%))	795 (93.6%)	393 (92.9%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	0.7
		95% two-sided CI	-2.0 ; 3.9
		p-value	0.621
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S2:** **COR-EE-D14, COR-EE-D42** **COR-ITT-D14, COR-ITT-D42**		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	809	400
	COR-EE-D14 (N (%))	800 (98.9%)	398 (99.5%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-0.6
		95% two-sided CI	-1.7 ; 0.8
		p-value	0.291
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	746	342
	COR-EE-D42 (N (%))	729 (97.7%)	337 (98.5%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-0.8
		95% two-sided CI	-2.4 ; 1.3
		p-value	0.374
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 14		

Descriptive statistics	Treatment group	PA	AL
	Number of subjects	849	423
	COR-ITT-D14 (N (%))	814 (95.9%)	405 (95.7%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	0.1
		95% two-sided CI	-2.1 ; 2.8
		p-value	0.911
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	849	423
	COR-ITT-D42 (N (%))	746 (87.9%)	346 (81.8%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	6.1
		95% two-sided CI	1.9 ; 10.5
		p-value	0.003
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S3: CRU-EE-D14, CRU-EE-D28, CRU-EE-D42 CRU-ITT-D14, CRU-ITT-D28, CRU-ITT-D42**		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	809	400
	CRU-EE-D14 (N (%))	800 (98.9%)	398 (99.5%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-0.6
		95% two-sided CI	-1.7 ; 0.8
		p-value	0.291
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	794	393
	CRU-EE-D28 (N (%))	775 (97.6%)	375 (95.4%)

Effect estimate per comparison		Comparison groups	PA – AL
		Difference	2.2
		95% two-sided CI	0.1 ; 4.9
		p-value	0.041
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	779	379
	CRU-EE-D42 (N (%))	693 (89.0%)	319 (84.2%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	4.8
		95% two-sided CI	0.7 ; 9.3
		p-value	0.021
Analysis population and time point description	ITT population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	849	423
	CRU-ITT-D14 (N (%))	814 (95.9%)	405 (95.7%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	0.1
		95% two-sided CI	-2.1 ; 2.8
		p-value	0.911
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	849	423
	CRU-ITT-D28 (N (%))	790 (93.1%)	383 (90.5%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	2.5
		95% two-sided CI	-0.6 ; 6.0
		p-value	0.116
Notes	CI = Confidence Interval		

Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	849	423
	CRU-ITT-D42 (N (%))	709 (83.5%)	328 (77.5%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	6.0
		95% two-sided CI	1.4 ; 10.8
		p-value	0.010
Analysis description	**Secondary analysis S4:** **Proportion of aparasitaemic patients and time to parasite clearance**		
Analysis population and time point description	ITT population		
Kaplan-Meier estimate	Treatment group	PA	AL
	Number of subjects	849	423
	Aparasitaemic at Day 1 (% (95% CI))	66.0 (62.8 ; 69.1)	52.0 (47.3 ; 56.8)
	Aparasitaemic at Day 2 (% (95% CI))	95.5 (94.0 ; 96.8)	95.3 (93.0 ; 97.0)
	Aparasitaemic at Day 3 (% (95% CI))	96.9 (95.6 ; 97.9)	97.9 (96.1 ; 98.9)
	Median time to parasite clearance (hours (95% CI))	23.9 (23.9 ; 23.9)	24.0 (23.9 ; 24.1)
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S5:** **Proportion of afebrile patients and time to fever clearance**		
Analysis population and time point description	ITT population		
Kaplan-Meier estimate	Treatment group	PA	AL
	Available observations	631	328
	Afebrile at Day 1 (% (95% CI))	86.4 (83.6 ; 88.9)	85.7 (81.6 ; 89.2)
	Afebrile at Day 2 (% (95% CI))	96.5 (94.9 ; 97.7)	97.0 (94.7 ; 98.4)
	Afebrile at Day 3 (% (95% CI))	97.0 (95.4 ; 98.1)	97.9 (95.8 ; 99.0)
	Median time to fever clearance (hours (95% CI))	8.0 (7.9 ; 8.0)	8.0 (7.9 ; 15.5)
Notes	CI = Confidence Interval Available observations = Subjects in the ITT population with fever at baseline		
Analysis description	**Secondary analysis S6:** **Proportion of patients with gametocytes by time points**		

Analysis population and time point description	ITT population		
Descriptive statistics Number of subjects with gametocytes (N (%))	Treatment group	PA	AL
	Number of subjects	849	423
	Screening	60 (7.1%)	23 (5.5%)
	Day 0 / H0	66 (7.8%)	22 (5.2%)
	Day 0 / H8	67 (8.0%)	27 (6.4%)
	Day 0 / H16	79 (9.5%)	22 (5.2%)
	Day 1 / H24	87 (10.5%)	28 (6.7%)
	Day 1 / H32	89 (11.3%)	23 (5.8%)
	Day 1 / H40	67 (9.7%)	22 (6.0%)
	Day 2 / H48	56 (8.9%)	16 (4.8%)
	Day 2 / H56	50 (8.2%)	14 (4.6%)
	Day 2 / H64	53 (8.8%)	15 (5.0%)
	Day 3	67 (8.2%)	16 (3.9%)
	Day 7	65 (7.9%)	13 (3.2%)
	Day 14	38 (4.7%)	6 (1.5%)
	Day 21	25 (3.1%)	3 (0.8%)
	Day 28	8 (1.0%)	0
	Day 35	3 (0.4%)	0
	Day 42	0	0
Analysis population and time point description	Efficacy Evaluable population		
Descriptive statistics Number of subjects with gametocytes (N (%))	Treatment group	PA	AL
	Number of subjects	784	386
	Screening	57 (7.3%)	19 (4.9%)
	Day 0 / H0	63 (8.0%)	18 (4.7%)
	Day 0 / H8	64 (8.2%)	24 (6.2%)
	Day 0 / H16	74 (9.4%)	20 (5.2%)
	Day 1 / H24	83 (10.6%)	26 (6.8%)
	Day 1 / H32	84 (11.3%)	22 (5.9%)
	Day 1 / H40	62 (9.5%)	21 (6.1%)
	Day 2 / H48	53 (8.9%)	16 (5.2%)
	Day 2 / H56	49 (8.5%)	14 (4.9%)
	Day 2 / H64	52 (9.0%)	15 (5.3%)
	Day 3	66 (8.5%)	15 (3.9%)
	Day 7	64 (8.2%)	12 (3.1%)
	Day 14	37 (4.8%)	6 (1.6%)
	Day 21	25 (3.2%)	3 (0.8%)
	Day 28	8 (1.0%)	0
	Day 35	3 (0.4%)	0
	Day 42	0	0

Table 17: Summary of Efficacy for trial SP-C-006-06

Title: A Phase III multi-centre, randomised, double-blind, double-dummy, comparative clinical study to assess the safety and efficacy of a fixed dose formulation of oral pyronaridine artesunate (180:60 mg tablets) versus chloroquine (155 mg tablet), in children and adult patients with acute *Plasmodium vivax* malaria			
Study identifier	SP-C-006-06		
Design	multicentre, randomised, double-blind, double-dummy, comparative study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		42 days not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	PA		Pyronaridine/Artesunate, 3 days, 228
	CQ		Chloroquine, 3 days, 228
Endpoints and definitions	Primary endpoint	CRU-EE-D14	Day 14 crude cure rate in EE population
	Secondary endpoints	S1: CRU-ITT-D14	Day 14 crude cure rate in ITT population
		S2: CRU-<POP>-<DAY>	Crude cure rate at days 28 and 42 in EE and ITT populations
		S3	Proportion of aparasitaemic patients and time to parasite clearance
		S4	Proportion of afebrile patients and time to fever clearance
Database lock	9 September 2008		

Results and Analysis

Analysis description	**Primary Analysis: CRU-EE-D14**		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	CQ
	Number of subjects	218	211
	CRU-EE-D14 (N (%))	217 (99.5%)	209 (99.1%)
Effect estimate per comparison	Primary endpoint	Comparison groups	PA – CQ
		Difference	0.5
		95% two-sided CI	-1.7 ; 3.0
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S1: CRU-ITT-D14**		
Analysis population and time point description	ITT population Day 14		
Descriptive statistics	Treatment group	PA	CQ
	Number of subjects	228	228

	CRU-ITT-D14 (N (%))	217 (95.2%)	212 (93.0%)
Effect estimate per comparison		Comparison groups	PA – CQ
		Difference	2.2
		95% two-sided CI	-2.3 ; 6.8
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S2: CRU-EE-D28, CRU-EE-D42 CRU-ITT-D28, CRU-ITT-D42**		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	CQ
	Number of subjects	208	198
	CRU-EE-D28 (N (%))	202 (97.1%)	192 (97.0%)
Effect estimate per comparison		Comparison groups	PA – CQ
		Difference	0.1
		95% two-sided CI	-3.5 ; 3.9
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	CQ
	Number of subjects	199	192
	CRU-EE-D42 (N (%))	190 (95.5%)	175 (91.1%)
Effect estimate per comparison		Comparison groups	PA – CQ
		Difference	4.3
		95% two-sided CI	-0.7 ; 9.6
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	CQ
	Number of subjects	228	228
	CRU-ITT-D28 (N (%))	202 (88.6%)	195 (85.5%)
Effect estimate per comparison		Comparison groups	PA – CQ
		Difference	3.1
		95% two-sided CI	-3.1 ; 9.3
Notes	CI = Confidence Interval		

Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	CQ
	Number of subjects	228	228
	CRU-ITT-D42 (N (%))	190 (83.3%)	178 (78.1%)
Effect estimate per comparison		Comparison groups	PA – CQ
		Difference	5.3
		95% two-sided CI	-2.0 ; 12.5
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S3: Proportion of aparasitaemic patients and time to parasite clearance**		
Analysis population and time point description	ITT population		
Kaplan-Meier estimate	Treatment group	PA	CQ
	Number of subjects	228	228
	Aparasitaemic at Day 1 (% (95% CI))	71.9 (66.1 ; 77.8)	29.8 (23.9 ; 35.8)
	Aparasitaemic at Day 2 (% (95% CI))	99.6 (98.7 ; 100)	84.6 (80.0 ; 89.3)
	Aparasitaemic at Day 3 (% (95% CI))	100 (100 ; 100)	93.4 (90.2 ; 96.6)
	Median time to parasite clearance (hours (95% CI))	23.0 (16.3 ; 23.5)	32.0 (31.8 ; 32.2)
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S4: Proportion of afebrile patients and time to fever clearance**		
Analysis population and time point description	ITT population		
Kaplan-Meier estimate	Treatment group	PA	CQ
	Available observations	175	166
	Afebrile at Day 1 (% (95% CI))	78.3 (72.2 ; 84.4)	57.2 (49.7 ; 64.8)
	Afebrile at Day 2 (% (95% CI))	89.1 (84.5 ; 93.8)	86.1 (80.9 ; 91.4)
	Afebrile at Day 3 (% (95% CI))	97.1 (94.7 ; 99.6)	95.2 (91.9 ; 98.4)
	Median time to fever clearance (hours (95% CI))	15.9 (15.7 ; 16.0)	23.8 (16.0 ; 24.0)
Notes	CI = Confidence Interval Available observations = Subjects in the ITT population with fever at baseline		

Table 18: Summary of Efficacy for trial SP-C-007-07

Title: A Phase III comparative, open-labelled, randomised, multi-centre clinical study to assess safety and efficacy of a fixed dose of oral pyronaridine artesunate granule formulation (60:20 mg) (paediatric PYRAMAX®) versus Coartem® (artemether lumefantrine) crushed tablets in infants and children with acute uncomplicated *Plasmodium falciparum* malaria			
Study identifier	SP-C-007-07		
Design	multicentre, comparative, randomised, open-labelled, parallel group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		42 days not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	PA		Pyronaridine/Artesunate, 3 days, 355
	AL		Artemether/Lumefantrine, 3 days, 180
Endpoints and definitions	Primary endpoint	P1	PCR-corrected ACPR at Day 28 in the PA group <=90% (EE population)
	Secondary endpoints	S1: COR-EE-D28 COR-ITT-D28	Day 28 PCR-corrected ACPR in EE and ITT populations
		S2: COR-<POP>-<DAY>	PCR-corrected ACPR at days 14 and 42 in EE and ITT populations
		S3: CRU-<POP>-<DAY>	Crude cure rate at days 14, 28 and 42 in EE and ITT populations
		S4	Proportion of aparasitaemic patients and time to parasite clearance
		S5	Proportion of afebrile patients and time to fever clearance
		S6	Proportion of patients with gametocytes by time points
Database lock	26 November 2008		

Results and Analysis

Analysis description	**Primary Analysis P1**		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	339	167
	COR-EE-D28 (N (%))	329 (97.1%)	165 (98.8%)
Effect estimate per comparison	Primary endpoint	p-value *	<0.001
Notes	* For the hypothesis that the ACPR in the PA group is <=90%		
Analysis description	**Secondary analysis S1: COR-EE-D28, COR-ITT-D28**		
Analysis population and time point description	Efficacy Evaluable population Day 28		

Descriptive statistics	Treatment group	PA	AL
	Number of subjects	339	167
	COR-EE-D28 (N (%))	329 (97.1%)	165 (98.8%)
Effect estimate per comparison	Between group comparison	Comparison groups	PA – AL
		Difference	-1.8
		95% two-sided CI	-4.3 ; 1.6
		p-value *	0.223
Notes	* Two-sided Chi-Square test for superiority CI = Confidence Interval		
Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	COR-ITT-D28 (N (%))	333 (93.8%)	167 (92.8%)
Effect estimate per comparison		p-value *	0.008
	Between group comparison	Comparison groups	PA – AL
		Difference	1.0
		95% two-sided CI	-3.2 ; 6.2
		p-value **	0.651
Notes	* For the hypothesis that the ACPR in the PA group is <=90% ** Two-sided Chi-Square test for superiority CI = Confidence Interval		
Analysis description	**Secondary analysis S2: COR-EE-D14, COR-EE-D42 COR-ITT-D14, COR-ITT-D42**		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	343	172
	COR-EE-D14 (N (%))	341 (99.4%)	172 (100%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-0.6
		95% two-sided CI	-2.1 ; 1.6
		p-value	0.316
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	AL

	Number of subjects	275	139
	COR-EE-D42 (N (%))	257 (93.5%)	133 (95.7%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-2.2
		95% two-sided CI	-6.5 ; 3.1
		p-value	0.359
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	COR-ITT-D14 (N (%))	344 (96.9%)	174 (96.7%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	0.2
		95% two-sided CI	-2.7 ; 4.2
		p-value	0.884
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	COR-ITT-D42 (N (%))	262 (73.8%)	135 (75.0%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-1.2
		95% two-sided CI	-8.7 ; 6.9
		p-value	0.765
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S3: CRU-EE-D14, CRU-EE-D28, CRU-EE-D42 CRU-ITT-D14, CRU-ITT-D28, CRU-ITT-D42**		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	343	172
	CRU-EE-D14 (N (%))	341 (99.4%)	172 (100%)

Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-0.6
		95% two-sided CI	-2.1 ; 1.6
		p-value	0.316
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	341	172
	CRU-EE-D28 (N (%))	305 (89.4%)	149 (86.6%)
Effect estimate per comparison		Comparison groups	AL
		Difference	2.8
		95% two-sided CI	-2.9 ; 9.4
		p-value	0.345
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	325	166
	CRU-EE-D42 (N (%))	249 (76.6%)	130 (78.3%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-1.7
		95% two-sided CI	-9.1 ; 6.4
		p-value	0.671
Analysis population and time point description	ITT population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	CRU-ITT-D14 (N (%))	344 (96.9%)	174 (96.7%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	0.2
		95% two-sided CI	-2.7 ; 4.2
		p-value	0.884
Notes	CI = Confidence Interval		

Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	CRU-ITT-D28 (N (%))	309 (87.0%)	151 (83.9%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	3.2
		95% two-sided CI	-2.9 ; 10.0
		p-value	0.321
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	CRU-ITT-D42 (N (%))	254 (71.5%)	132 (73.3%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-1.8
		95% two-sided CI	-9.5 ; 6.4
		p-value	0.664
Analysis description	**Secondary analysis S4: Proportion of aparasitaemic patients and time to parasite clearance**		
Analysis population and time point description	ITT population		
Kaplan-Meier estimate	Treatment group	PA	AL
	Number of subjects	355	180
	Aparasitaemic at Day 1 (% (95% CI))	49.3 (44.1 ; 54.5)	41.7 (34.5 ; 48.9)
	Aparasitaemic at Day 2 (% (95% CI))	94.6 (92.3 ; 97.0)	93.3 (89.7 ; 97.0)
	Aparasitaemic at Day 3 (% (95% CI))	96.1 (94.0 ; 98.1)	97.2 (94.8 ; 99.6)
	Median time to parasite clearance (hours (95% CI))	24.1 (24.0 ; 24.1)	24.2 (24.1 ; 32.0)
Notes	CI = Confidence Interval		
Analysis description	**Secondary analysis S5: Proportion of afebrile patients and time to fever clearance**		
Analysis population and time point description	ITT population		
Kaplan-Meier	Treatment group	PA	AL

estimate	Available observations	278	135
	Afebrile at Day 1 (% (95% CI))	86.3 (82.3 ; 90.4)	79.3 (72.4 ; 86.1)
	Afebrile at Day 2 (% (95% CI))	97.5 (95.6 ; 99.3)	94.1 (90.1 ; 98.1)
	Afebrile at Day 3 (% (95% CI))	98.6 (97.2 ; 100)	95.6 (92.1 ; 99.0)
	Median time to fever clearance (hours (95% CI))	8.1 (8.0 ; 8.1)	8.1 (8.0 ; 15.8)
Notes	CI = Confidence Interval Available observations = Subjects in the ITT population with fever at baseline		
Analysis description	**Secondary analysis S6:** **Proportion of patients with gametocytes by time points**		
Analysis population and time point description	ITT population		
Descriptive statistics Number of subjects with gametocytes (N (%))	Treatment group	PA	AL
	Number of subjects	355	180
	Baseline	44 (12.4%)	26 (14.4%)
	>0-24 hours	73 (20.6%)	39 (21.9%)
	>24-48 hours	63 (19.3%)	23 (13.4%)
	>48-72 hours	40 (15.1%)	16 (11.9%)
	>72 hours – Day 5	20 (18.0%)	6 (10.0%)
	Day 6 – 12	45 (13.0%)	16 (9.2%)
	Day 13 – 16	28 (8.3%)	6 (3.5%)
	Day 17 – 26	15 (4.5%)	2 (1.2%)
	Day 27 – 30	3 (0.9%)	2 (1.2%)
	Day 31 – 40	1 (0.3%)	0
	Day 41 – 44	0	0
	>Day 44	0	0
	Any post-baseline	95 (26.8%)	44 (24.7%)
	Any post-baseline (new occurrence)	53 (15.0%)	20 (11.2%)
Analysis population and time point description	Efficacy Evaluable population		
Descriptive statistics Number of subjects with gametocytes (N (%))	Treatment group	PA	AL
	Number of subjects	337	167
	Baseline	43 (12.8%)	24 (14.4%)
	>0-24 hours	71 (21.1%)	35 (21.0%)
	>24-48 hours	62 (19.9%)	22 (13.6%)
	>48-72 hours	40 (15.6%)	15 (11.7%)
	>72 hours – Day 5	19 (17.9%)	6 (10.9%)
	Day 6 – 12	44 (13.1%)	16 (9.6%)
	Day 13 – 16	28 (8.5%)	6 (3.6%)

	Day 17 – 26	15 (4.5%)	2 (1.2%)
	Day 27 – 30	3 (0.9%)	2 (1.2%)
	Day 31 – 40	1 (0.3%)	0
	Day 41 – 44	0	0
	>Day 44	0	0
	Any post-baseline	92 (27.3%)	40 (24.0%)
	Any post-baseline (new occurrence)	51 (15.1%)	18 (10.8%)

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

Plasmodium vivax

The applicant provided the pooled analysis of the 2 *Plasmodium vivax* studies. In the pooled EE population, the crude cure rate on Day 14 was 99.6% in the PA group and 100.0% in the chloroquine group. The 2-sided 95% CI for the treatment group difference ranges from -2.4% to 1.3% indicating that, with a probability of 95%, PA is no more than 2.4% worse than chloroquine, i.e., non-inferiority was clearly demonstrated assuming the non-inferiority margin of 10% that was applied in study SP-C-006-06. In the pooled ITT population, the crude cure rate on Day 14 was 95.5% in the PA group and 93.4% in the chloroquine group, with non-inferiority of PA to chloroquine concluded (treatment difference 2.0 , 95% CI -2.2; 6.4).

Examining the Day 14 crude cure rate based on age category of <12 years of age and >12 years of age, there are no differences in the % of subjects cured. Likewise in the Kaplan-Meier Estimates of PCT according to age for the same categories, no difference between median parasite clearance time is seen.

The effects on PCR-corrected cure rate is sustained to Day 42 in the exploratory EE and ITT populations.

2.5.3. Discussion on clinical efficacy

Plasmodium falciparum

Design and conduct of clinical studies

In *Plasmodium falciparum* malaria, the studies were conducted in parallel groups, using a non-inferiority design, to compare a 3 days treatment course of Pyramax to reference ACTs: mefloquine + artesunate or artemether/lumefantrine. These comparators can be considered as appropriate as they are currently the most commonly recommended first line therapies in acute *Plasmodium falciparum* malaria in the endemic area where the studies were conducted (Africa and South East Asia).

According to the protocol of the studies, the primary end point of the 3 studies was initially based on Day 28 assessment, being in line with the WHO protocol for conduct of trials of antimalarial drugs during the period of the trial conduct. The three studies showed that the pyronaridine/artesunate (PA) combination was at least as effective on Day 28 on the primary end point ACPR rates (PCR-corrected and Crude). However, considering the long half lives of the non- artemisinin partner component of the ACTs been used, the primary analysis performed at Day 28 doesn't reflect the true cure rates since recrudescences remain minimal at that time point. Also, the half life of lumefantrine is much shorter than pyronaridine (around 3 to 6 days in patients with malaria). Then, if the more rapidly eliminated

treatment is compared with a slowly eliminated one, the results tend to be biased in favour of the slowly eliminated treatment as recrudescences can emerged more rapidly in the group receiving the medicinal compound with the shortest half life. Therefore, considering the half life of pyronaridine and mefloquine being longer than one week (pyronaridine: T1/2 around 11-16 days; mefloquine: T1/2 around 21 days), the follow up should ideally have been approximately 63 days to allow sufficient time to "capture" all the treatment failures (recrudescences). However, no efficacy data were provided after Day 42 in the submitted studies. Therefore, only 42 days follow up is available for the present application for Pyramax.

As the relevant time point is Day 42, the applicant newly defined the EE analysis by extending the exclusion criteria initially adopted for Day 28 EE population to the Day 42 EE population (i.e. patients with missing data at Day 42, and not rated as previous treatment failures, were excluded from Day 42 EE population). Although less conservative, this redefined Day 42 EE population was logical as handling of missing data became homogeneous through Day 42 whilst the previous analysis mixed different handling of missing data.

Efficacy data and additional analyses

Doubts were initially raised with regards to non-inferiority of PA as compared to MQ+AS as, based on results from Study SP-C-004-06, statistical non inferiority was not fully established on PCR-corrected ACPR at Day 42 in the Efficacy Evaluable population originally defined by the applicant. After the EE population had been redefined, non inferiority appeared consistently at Day 42 with respect to ACPR (PCR-corrected and crude) in the EE (revised) and ITT (unchanged) populations. However, the rate of treatment failures/recrudescences tends to be higher in the PA group as compared to MQ+AS group i.e. 5.3% vs. 2.9 % respectively, in the EE population (but rates are similar between the groups in the ITT population). These results are close to Kaplan-Meier estimates of cumulative risks of recrudescences through Day 42 (PA: 5.3 % vs. MQ+AS: 2.5%). As a possible explanation of those statistical results, the higher rate of recrudescences that was observed in the Cambodian site (Pailin) could have impacted on the results from the global population. Indeed, at Pailin site (counting for 20% out of the total population included), a higher rate of recrudescences was observed with PA as compared to MQ+AS and also as compared to the population from all the other sites. Also, consistently with the emerging reduced susceptibility to artemisins that has been reported in the Cambodia-Thailand border region (ref.: Noedl H, N Engl J Med 2008; Dondorp AM, N Engl J Med, 2009), slower parasite clearance time was observed at this site (i.e. 64 vs. 31-32 hours = almost a 2-fold increase in median parasite clearance time as compared to the other sites included). The applicant states that as pyronaridine half-life in adult malaria patients is approximately 14-16 days compared with around 3 weeks for mefloquine, it is possible that the different pharmacokinetic/pharmacodynamic properties of pyronaridine and mefloquine allowed quiescent parasites to re-emerge earlier with PA than with MQ+AS in an area of resistance/decrease of efficacy of artesunate. As such, only a study with a longer follow-up period of at least 63 days could confirm this hypothesis. It is pointed out that pyronaridine as partner to artesunate did not appear to show any benefit as compared to mefloquine with respect to recrudescences and in terms of preventing resistance to artemisinins.

Non-inferiority of PA tablets as compared to AL was consistently shown at Day 42 on ACPR (PCR-corrected and Crude) in the EE and ITT analyses in the tablets study SP-C-005-06 conducted in adults and children weighing more than 20 kg. Treatment failures and recrudescences rates were similar in both treatments groups. Cambodia-Thailand border region sites were not included in this study. It was noticed that according to the recommendations, AL should have been taken with food or a milky drink to achieve optimal absorption of lumefantrine; thus, the appropriateness of AL taken with water as a comparator in this study was questioned. Basically, it was not so clear whether the patients in the Pyramax studies were recommended to take fatty foods with AL, and indeed how many did so. In

response to the issue raised, the applicant collected some exposure data in study SP-C-005-06 and great variability appear in exposure levels. Overall though, it can be recognised that the efficacy of AL in study SP-C-OO5-06 was high, suggesting that, whatever the conditions of administration have been, the antimalarial efficacy was acceptable. As such, the conditions of administration of AL in SP-C-005-06 clinical study cannot be considered to be worse than what they will be in real life practice and then it can be considered that they resemble "real life efficiency" of AL in endemic area. This issue has been considered solved and demonstration of non inferiority can be accepted.

Non-inferiority cannot be recognised in the paediatric study SP-C-007-07, using PA granule formulation as compared to AL dispersible tablets in children < 20 kg since the lower limit of the between group differences are consistently between -10 % and -5%. The – 10 % non inferiority limit initially predefined by the applicant is too low and cannot be recognised as acceptable. This study, which included young children less than 12 years, showed a lower cure rate with a higher rate of failures/recrudescence as compared to the studies conducted using the tablets in patients > 20 kg. As very young children (less than 12 years) were enrolled in this study, the explanation of the applicant that younger children had a lower immunity is plausible. But, importantly, the qualitative and quantitative composition of the granules significantly differs from tablets and bioequivalence has not been established. It can neither be ruled out that the absorption is lower with granules as compared to tablets. Also, it cannot be excluded that PK profile in young children differs from adults. No extrapolation can be made from study SP-C-007-07 to the tablets application.

Overall, no extrapolation can be made in young children less than 20 kg body weight on safety grounds (systemic exposure unknown with the granules) nor on efficacy grounds (less favourable results in this younger population). The available data do not allow us to establish the benefit/risk balance of Pyramax use under 20 kg body weight. The indication initially claimed by the applicant for children from 15 to 20 kg in *P. falciparum* cannot be supported by available data and therefore the indication has been restricted to patients with body weight > 20 kg pending additional studies in the paediatric population.

The applicant has provided sub-analysis according to the level of endemic malaria based on *Plasmodium falciparum* parasite rate (PfPR) as an indirect marker of immunity in the local population, pooling all clinical phase III studies conducted with Pyramax (data not shown in this overview). The results showed a slight trend towards lower cure rates and slower parasite clearance time in the lower risk regions (semi-immune or immune population with low PfPR i.e. > 5% and ≤ 40%) as compared to the high-risk immune regions (PfPR is > 40%). The results were of the same extent as observed for the comparison products. It can be agreed with the applicant that these results are still acceptable to the use of Pyramax in regions with diverse malaria endemicity.

Finally, the gametocytes clearance time consistently appeared longer in the PA groups as compared to MQ+AS or AL in all studies conducted in *Plasmodium falciparum* malaria. These observations are worrying with regards to transmission, especially in areas where lower sensitivity of *P. falciparum* to artesunate begins to emerge i.e. Western Cambodia. The applicant intends to perform further comparative trials assessing the viability of the gametocytes and mosquito infectivity after Pyramax treatment at 2 African sites (SP-C-013-11). Information on consistently longer *P. falciparum* gametocytes clearance time and carriage that was observed in clinical trials in the Pyramax treated groups as compared to mefloquine plus artesunate or artemether/lumefantrine treated groups is included in section 5.1 of the SmPC.

Plasmodium vivax

Design and conduct of clinical studies

In the Phase III programme of Pyramax for the treatment of *P. vivax* malaria, a total of 456 subjects were equally randomised to the PA and chloroquine treatment groups in Study SP-C-006-06 and a total of 30 subjects were equally randomised to the PA and chloroquine groups in Study-SP-C- 008-07. Inclusion criteria were similar across the two studies.

The efficacy endpoint "crude cure rate", defined as "no parasitaemia irrespective of axillary temperature" is acceptable and in agreement with the WHO protocol. While the Day 14 data endpoint was considered appropriate when the study was undertaken, nowadays the longer term endpoint at D28 (or even D42) is considered equally valid.

At the time the trials SP-C-006-06 and SP-C-008-07 were implemented, *Plasmodium vivax* resistance to chloroquine was not an issue at the sites where studies were conducted (low level of resistance to chloroquine); otherwise a protocol including a chloroquine-arm would not have been acceptable to the local Ethics Committees. According to WHO updated recommendations (Guidelines for the treatment of malaria-2010), *Plasmodium vivax* remains sensitive in most of South-East Asia and Indian subcontinent (with resistance to chloroquine is confined largely to parts of Indonesia).

Efficacy data and additional analyses

Based on study SP-C-006-06, conducted in *Plasmodium vivax* malaria, pyronaridine/artesunate (180:60 mg) tablet combination was shown to be at least as effective (in terms of cure rates) as chloroquine at sites in Cambodia, India, Indonesia (Maumere), and Thailand. Time to parasite clearance was statistically significantly shorter in the PA group than in the chloroquine group (median: 23.1 vs. 32.0 hours, p=0.0071). However, only 13 PA and 14 CQ children less than 12 years were included. The Korean study SP-C-008-07 had the same design but it was prematurely terminated by the sponsor and included only 15 PA adults (from 17 to 56 years old). The applicant provided the pooled analysis of the 2 *Plasmodium vivax* studies but this add little to the overall effect size and the pooling of data was not of much value (especially with respect to paediatric data).

The results of these studies support the relative efficacy of PA over CQ in adults, but although 100 % efficacy was observed in the paediatric sample size from the available study, data remain sparse in the paediatric most vulnerable population prone to severe outcomes with *Plasmodium vivax*. Also, it is noted that severe cases i.e. patients with < 8g/dl haemoglobin were excluded from all *Plasmodium vivax* studies. Moreover, no data are available with Pyramax in areas where chloroquine-resistance of *Plasmodium vivax* has been described as a real concern i.e. mostly in Northeastern Papua, close to the border between Indonesia and Papua New Guinea. The applicant intends to conduct a study in infant and children aged > 6 month to 12 years with *Plasmodium vivax* malaria in Papua New Guinea using a paediatric granule formulation of pyronaridine/artesunate combination (study SP-C-011-10).

A statement is included in SmPC section 5.1, to indicate the age of the population included in the *Plasmodium vivax* studies (mentioning only 13 PA children vs. 15 CQ). It is also clarified that the study was conducted exclusively in areas of low chloroquine resistance.

Additional expert consultation

The advice of an Ad-Hoc Expert Group was sought on the following aspects:

Efficacy & Drug Resistance

1. Expert opinion was sought on the higher rate of recrudescences as reported at Day 42 in Cambodia site (Pailin) with Pyramax as compared to the other countries while there was no statistical difference Cambodia and all other countries in the MQ+AS group (SP-C-004-06)

   Prolonged parasite clearance times following treatment with ACTs (reflecting emergence of *P. falciparum* tolerance to artemisinins) have been observed along the Thai-Cambodian border.

   The expert group remarked that in that region, *P. falciparum* resistance is very fluent and dynamic and as mefloquine resistance locally reappeared since 2006, it cannot be excluded that the rate of recrudescences with MQ+AS combination could be higher now than what was observed in the study SP-C-004-06 (conducted from January 2007 to October 2008), leading to probable different results between the treatment groups.

2. In phase III clinical studies longer carriage of gametocytes was consistently associated with Pyramax in comparison to MQ+AS and AL. It was questioned if this finding would limit the usefulness of Pyramax in certain areas

   The experts concurred that the longer carriage of gametocytes with Pyramax is an accepted finding. It causes marginally increased exposure in mosquitoes and thus in terms of transmission would probably have a small effect. However, experts confirmed that in absence of an infectivity study, no conclusion can be reached.

   (Please note that infectivity will be studied by applicant, within trial SP-C-013-11).

3. It was asked if experts consider that efficacy data in adults allow to extrapolate to efficacy in children in *P. vivax* malaria.

   According to the experts, *Plasmodium vivax* efficacy/(safety) results observed from study SP-C-006-06 can be extended to children more than 20 kg body weight as no difference would be expected on PK and safety grounds and with respect to acquired immunity in endemic area in the paediatric population more than 20 kg body weight as compared to the characteristic of the largest part of the population that was included in malaria trials.

   It was noted that further data are expected in young children in Papua New Guinea (high level of resistance of *P. vivax* to chloroquine) that will better address the potential benefit of Pyramax in *Plasmodium vivax* malaria in endemic area.

In addition, the Expert Group suggested confined introduction of Pyramax in first instance to delineated areas of SE Asia with rapidly emerging *Plasmodium falciparum* resistant to antimalarial drugs and with low transmission. This suggestion relates to the threat of artemisinin-resistant malaria raised by delayed parasites clearance time observed in Thai-Cambodian border region as compared to the other endemic areas.

The need for alternative partners in ACT in this region, in order to prevent loss of artemisinins due to resistance, is appreciated within the "Global Plan for Artemisinin Resistance Containment Project" recently launched by WHO.

Dose changing in the SmPC:

In the phase III studies conducted with the tablets, the lowest mg/kg doses administered (≤ 8.5:2.8 mg/kg per day) resulted in lower cure rates for both P. falciparum (PCR-corrected ACPR at Day 42 and recrudescence rates) and P. vivax (crude cure rate at Day 28) as compared to the higher dosing groups.

The issue relating to a higher incidence of treatment failures in the patients who received the lowest mg/kg doses (i.e. < 9mg/kg Pyronaridine) led to a recommendation to change the posology in the SmPC from 1 to 2 tablets in the 24 kg and 25 kg weighing subjects as they were those that had received the lowest doses with 1 tablet per day (i.e. = PP: 7.5 and 7.2 mg/kg/dose respectively; AS: 2.5 and 2.4 mg/kg/dose, respectively). This translates in a daily actual dose of PP:AS: 14.4 :4.8 mg/kg for patients weighing 25 kg and PP:AS 15: 5 mg/kg for patients weighing 24 kg (instead of 7.2:2.4 mg/kg per day and 7.5:2.5 mg/kg per day, respectively).

This can be accepted as it can be agreed that consistent efficacy results were observed throughout the actual dose mg/kg range above 8.5:2.8 mg/kg per day, and that this dosing was already covered in the tablets phase III studies (6.9:2.4 mg/kg per day to 13.8:4.6 mg/kg per day).

2.5.4. Conclusions on the clinical efficacy

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

Study SP-C-011-10: Phase IIIB (*P. vivax*), randomised, open-label, comparative clinical study to assess the safety and efficacy of a fixed-dose granule formulation of pyronaridine/artesunate (60:20 mg sachet) versus a fixe-dose formulation of artemether/lumefantrine dispersible tablets, in infants and children > 6 months and ≤ 12 years of age (≥ 5 kg and < 25 kg body weight) with acute uncomplicated *Plasmodium vivax* and mixed infections of malaria. This will be conducted in Papua New Guinea (3 sites). The applicant plans to collect PK data in children from this study.

Study SP-C-013-11: A multicenter study to assess the long term safety and efficacy of repeated dose of Pyramax in patients with *Plasmodium falciparum* malaria. To be conducted in Africa. Study initiation had been planned in October 2011 and interim data would be available on December 2012.

Mosquito infectivity and feeding trials (including children) after PA treatment will be studied in two sites from this study (methodology of these investigations are in process to be finalised).

These measures are noted in the RMP.

2.6. Clinical safety

Considering that the design (e.g. population, dosing regimen) of the Phase I studies was either single dose or at different doses from those used in the Phase III studies, and the small number of subjects that received 3 doses of pyronaridine + artesunate (PA), these studies were not pooled.

The primary pooling of studies is based on the Phase II and Phase III studies conducted in infants, children, and adult subjects with acute uncomplicated *P. falciparum* or *P. vivax* malaria (all Phase II/III studies population).

The doses tested in the Phase II studies correspond to the actual dosing calculated in the Phase III studies; therefore, the safety data collected under the different dosages were pooled. No distinction was made between the tablet and granule formulations; both were pooled together.

A subpopulation (Phase II/III *P. falciparum* population) was based on the pooling of Phase II and Phase III studies conducted in subjects with acute uncomplicated *Plasmodium falciparum* malaria only (i.e. excluding SP-C-006-06).

Although not included in the original statistical analysis plan, summary tables were generated for a third subpopulation, all Phase III tablet studies population, which was based on the pooling of the Phase III studies in which the tablet formulation of PA was administered (SP-C-004-06, SP-C-005-06, and SP-C-006-06).

All integrated safety analyses were performed on randomised subjects who received any amount of study drug. Subjects were analysed as treated.

Study SP-C-008-07 was submitted during evaluation of the Article 58 (EC) 726/2004 procedure. The safety aspects of this study (which enrolled 30 patients) are not further discussed.

Patient exposure

A total number of 2948 subjects received at least 1 dose of PA across the completed phase I, phase II, and phase III studies. This number excludes subjects from the recently submitted study (SP-C-008-07). Total exposure to pyronaridine/artesunate (PA) in the 2 phase II and 4 phase III trials amounted to 2815 patients, whereas the comparator groups (mefloquine/artesunate [MQ+AS], arthemeter/lumafantrine [AL] or chloroquine) included 1 254 patients. Most of these studies included *P. falciparum* infected patients, only one study included *P. vivax* infected patients (n = 456).

In the PA group (once daily dosing), mean dosage was 9.75 mg/kg/dose for PP and 3.25 mg/kg/dose for AS (actual range of study drug received by subjects was 4.2 - 16.3 mg/kg/dose PP and 1.4 - 5.4 mg/kg/dose AS). Mean total dose was 29.16 mg/kg for PP and 9.72 mg/kg for AS (actual range of study drug received by subjects was 6.1 - 54.8 mg/kg PP and 2.0 - 18.3 mg/kg AS).

In the Phase II/III studies, demographic and baseline characteristics data were similar across treatment groups. Approximately two-thirds of the PA and all comparators groups were male (66.0 % and 64.5 %, respectively). There were approximately equal numbers of Black subjects and Asian/Oriental subjects in the PA group. The majority of subjects in each treatment group were ≥ 5 years of age (93.5 % in the PA group vs. 94.3 % in the comparators). In the PA, group, 31.1 % were aged under 12 years.

Adverse events

The majority of patients in phase II/III experienced at least one AE of any causality (see the table below).

Table 19: Overview of Treatment-Emergent Adverse Events – All Phase II/III Studies Population

	PA (N=2815)		MQ + AS (N=423)		AL (N=603)		Chloroquine (N=228)		All Comparators (N=1254)	
Subjects with:	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
≥1 AE	1611	(57.2)	190	(44.9)	384	(63.7)	72	(31.6)	646	(51.5)
≥1 treatment-related AE[a]	708	(25.2)	94	(22.2)	203	(33.7)	23	(10.1)	320	(25.5)
≥1 SAE	18	(0.6)	3	(0.7)	2	(0.3)	0	(0.0)	5	(0.4)
≥1 treatment-related SAE	1	(<0.1)	2	(0.5)	0	(0.0)	0	(0.0)	2	(0.2)
≥1 severe or life-threatening AE	39	(1.4)	23	(5.4)	7	(1.2)	2	(0.9)	32	(2.6)
≥1 AE with outcome of death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
≥1 AE leading to study drug discontinuation	30	(1.1)	4	(0.9)	8	(1.3)	2	(0.9)	14	(1.1)
≥1 AE leading to withdrawal from study	44	(1.6)	4	(0.9)	9	(1.5)	0	(0.0)	13	(1.0)

a. Possible, probable, definite, or missing relationship to study drug.

Cross Reference: Statistical Table 4.1.1

The most frequently affected system organ classes were infections and infestations (mainly upper respiratory tract infections, nasopharyngitis and bronchitis), gastrointestinal disorders (mainly vomiting, abdominal pain, diarrhoea and nausea), investigations (mainly ALT/AST increased/abnormal, transaminases increased, platelet count increased, eosinophil count increased and haemoglobin decreased) and nervous system disorders (mainly headache).

The most frequently reported treatment-emergent AEs for PA patients, regardless causality, were headache (10.6 %), cough (5.9 %), anaemia (4.5 %) and vomiting (4.4 %).

For some AEs, higher incidences were reported for PA-patients:

- anaemia (4.5 % versus 2.9 % for all comparators),
- AST increased (2.2 % versus 1.2 % for all comparators),
- ALT increased (1.9 % versus 0.2 % for all comparators),
- transaminases increased (1.6 % versus 0.6 % for all comparators),
- eosinophil count increased (2.1 % versus 0.6 % for all comparators),
- malaria (1.2 % versus 0 for all comparators),
- *P. falciparum* infection (0.7 % versus 0 for all comparators).

About one quarter of patients experienced AEs considered as drug-related (DR-AEs) (25.2 % PA and 25.5 % all comparators). The rate was highest in the AL-group (33.7 %) and lowest in the chloroquine-group (10.1 %). The most frequently reported DR-AEs for PA patients were headache (3.0 % *versus* 2.9 % for all comparators), eosinophilia (2.5 % *versus* 2.4 % for all comparators) and vomiting (2.2 % *versus* 2.0 % for all comparators).

Table 20: Treatment-Emergent Adverse Events Considered to be Study Drug-Related Occurring in ≥ 1.0 % of Subjects in Any Treatment Group – All Phase II/III Studies Population

Preferred Term	PA (N=2 815) n (%)	MQ + AS (N=423) n (%)	AL (N=603) n (%)	Chloroquine (N=228) n (%)	All comparators (N=1 254) n (%)
≥1 treatment-related AE	708 (25.2)	94 (22.2)	203 (33.7)	23 (10.1)	320 (25.5)
Blood and lymphatic system disorders					
Anaemia	45 (1.6)	9 (2.1)	14 (2.3)	0 (0.0)	23 (1.8)
Basophilia	6 (0.2)	8 (1.9)	1 (0.2)	0 (0.0)	9 (0.7)
Eosinophilia	70 (2.5)	4 (0.9)	24 (4.0)	2 (0.9)	30 (2.4)
Lymphocytosis	20 (0.7)	0 (0.0)	16 (2.7)	0 (0.0)	16 (1.3)
Neutropenia	53 (1.9)	0 (0.0)	27 (4.5)	0 (0.0)	27 (2.2)
Ear and labyrinth disorders					
Vertigo	14 (0.5)	7 (1.7)	4 (0.7)	0 (0.0)	11 (0.9)
Gastrointestinal disorders					
Abdominal pain	39 (1.4)	2 (0.5)	15 (2.5)	0 (0.0)	17 (1.4)
Diarrhoea	18 (0.6)	6 (1.4)	3 (0.5)	0 (0.0)	9 (0.7)
Vomiting	63 (2.2)	7 (1.7)	14 (2.3)	4 (1.8)	25 (2.0)
Infections and infestations					
Upper respiratory tract infection	18 (0.6)	0 (0.0)	8 (1.3)	0 (0.0)	8 (0.6)
Urinary tract infection	6 (0.2)	0 (0.0)	6 (1.0)	0 (0.0)	6 (0.5)
Investigations					
Alanine aminotransferase increased	41 (1.5)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Aspartate aminotransferase increased	48 (1.7)	1 (0.2)	11 (1.8)	0 (0.0)	12 (1.0)
Blood albumin decreased	19 (0.7)	0 (0.0)	16 (2.7)	0 (0.0)	16 (1.3)
Blood creatine phosphokinase increased	15 (0.5)	3 (0.7)	3 (0.5)	6 (2.6)	12 (1.0)
Blood creatinine decreased	7 (0.2)	0 (0.0)	7 (1.2)	0 (0.0)	7 (0.6)
Blood glucose decreased	29 (1.0)	0 (0.0)	15 (2.5)	0 (0.0)	15 (1.2)
Blood potassium increased	16 (0.6)	1 (0.2)	6 (1.0)	0 (0.0)	7 (0.6)
Haemoglobin decreased	28 (1.0)	4 (0.9)	6 (1.0)	0 (0.0)	10 (0.8)
Platelet count increased	40 (1.4)	3 (0.7)	14 (2.3)	0 (0.0)	17 (1.4)
Transaminase increased	35 (1.2)	2 (0.5)	4 (0.7)	0 (0.0)	6 (0.5)
Metabolism and nutrition disorders					
Anorexia	25 (0.9)	8 (1.9)	7 (1.2)	2 (0.9)	17 (1.4)
Nervous system disorders					
Dizziness	17 (0.6)	20 (4.7)	1 (0.2)	5 (2.2)	26 (2.1)
Headache	84 (3.0)	13 (3.1)	20 (3.3)	3 (1.3)	36 (2.9)

For some Drug Related -AEs, higher incidences were reported for PA-patients: ALT increased (1.5 % *versus* 0.2 % for all comparators), AST increased (1.7 % *versus* 1.0 % for all comparators but similar to AL-group [1.8 %]) and transaminases increased (1.2 % *versus* 0.5 % for all comparators).

Serious adverse event/deaths/other significant events

No subject died.

No SAEs were reported in the Phase I studies.

The percentage of subjects with SAEs ranged from 0.0 % to 0.7 % across treatment groups (lowest for chloroquine [0] and highest for MQ+AS [0.7 %]). The incidence of SAEs was 0.6 % in the PA-group (18/2 815).

The most frequently reported SAE in the PA-group were related to the SOC Infections and infestations (diverse AEs including malaria, typhoid fever, urinary tract infection). No individual AEs were more frequently reported than once or twice.

Among all SAEs observed during the phase II/III clinical program, only 3 patients reported SAEs considered as treatment-related:

- 1 PA-patient: hepatic enzyme increased, incomplete abortion and urinary tract infection (negative urinary hCG at screening, history of spontaneous abortion, pregnancy discovered at D11 of treatment, bleeding occurred soon after D14),
- 2 MQ + AS-patients: 1 grand mal convulsion and 1 convulsion (both patients had no history of epilepsy or convulsion).

Immunological events

The incidence of these events was low and was similar to the comparators during the clinical programme. However, in the Phase II/III programme, Pyramax was only administered as a single 3-day course. Nevertheless, from the data available, immunological events did not appear as a safety concern. Cases of potential hypersensitivity after repeated use of the combination will have to be monitored during the post-marketing period.

Laboratory findings

Haematology

During the all phase II/III studies population, there were:

- decreases from baseline in haemoglobin (Day 3 and 7), with corresponding changes in haematocrit and red blood cells (RBCs),
- falls in neutrophils associated with mean increases from baseline in lymphocytes and eosinophils in each treatment group,
- across treatment groups, 53.0 - 64.5 % of patients had low platelets at baseline; platelet count rose during treatment in all treatment groups.

The majority of patients in PA-group and comparator-groups had a fall in haemoglobin between 0 and 2 g/dl compared with baseline on days 3 and 7. Incidences of elevations in eosinophil count increased from D3 to D28 in all treatment groups (e.g. for PA: 39.9 % on D3 to 51.7 % on D28).

From the data available, difference between the percentage differentials for white cell components can be observed. The total WBC remained rather stable whereas neutrophils decreased and then lymphocytes and eosinophils increased. But changes from baseline in % and absolute values of the total WBC and components appeared similar for pyronaridine/artesunate and other comparators.

Regarding increases in eosinophils, the assessment is confounded by several factors. Indeed, 1) a publication[1] (Davis TME) reported results from a study performed in Thai patients which suggested that blood eosinophil count may increase during malaria convalescence, and 2) patients treated in the studies currently reviewed are from areas where intestinal parasites infestations are common.

[1]Davis TME et al. Changes in the peripheral blood eosinophil count in falciparum malaria. Acta Tropica 1991; 48:243-245.

Data from clinical studies performed with PA did not reveal any definite cytotoxicity on WBC or components. However, PA treatment duration was only 3 days and no repeated treatments were administered. In addition, the applicant did not discuss whether haematological abnormalities noted during the clinical programme were rather isolated or associated with other AEs or biological abnormalities.

No major differences in mean changes in platelet counts from baseline were observed between treatment groups after 3 days of treatment. It could not be clearly evaluated whether haematological abnormalities noted during the clinical programme had been rather isolated or associated with other AEs or biological abnormalities. This issue will have to be monitored during marketing period.

Finally, only few patients with haemoglobinopathy were identified in the clinical programme of Pyramax. This low number precludes any definite conclusion about the safety profile of the combination pyronaridine/artesunate in this special population. Hence, cases of potential haematological disorders and the safety profile in patients with haemoglobinopathy after repeated use of the combination treatment will have to be monitored during post-marketing follow-up (routine pharmacovigilance).

Biochemistry

In one phase I (adult healthy volunteers) bioequivalence single dose, two way cross-over study (SP-C-009-07) comparing the to-be-marketed tablet with the tablet formulation used in the phase III studies, 3 cases of increase in alanine aminotransferase (ALT > 3x ULN and < 10x ULN) were observed for three subjects (out of 39) after the second dose (following the wash out period). These were deemed clinically relevant by the investigator and reported as AEs. One of the subjects also showed a concomitant increase in gamma-GT. Increases in transaminases levels did not appear to be associated with significant increases in eosinophil count (that normally would be expected as elevated in case of underlying hypersensitivity mechanism).

In overall Phase II/III studies population, with the exception of ALT and AST, mean changes from baseline in biochemistry parameters were similar in the 4 treatment groups and the comparators group.

However, incidences of patients with treatment-emergent ALT or AST ≥ 3x, ≥ 5x or ≥ 10x ULN was greater in the PA group compared to each of the other treatment groups.

The percentage of patients in the PA-group with shifts from normal or low baseline value to high ALT or AST values was greater than in each of the other treatment groups on days 3 and 7 (PA-group: 9.9 % and 18.7 % for ALT on days 3 and 7 and 19.6 % and 20.4 % for AST compared to a range from 4.1 % to 10.5 % for the all comparators-group).

On day 28, no PA-patient had a Grade 3 (5x – 10x ULN) or 4 (> 10x ULN) ALT/AST value. In most cases, increase in transaminases resolved or improved by time of final evaluation.

In overall Phase II/III studies population, 6 PA-patients(0.2%) and 2 AL-patients (0.3%) had peak ALT ≥ 3x ULN and/or peak AST ≥ 3x ULN and peak total bilirubin ≥ 2x ULN, reaching the definition of the Hy's law. Out of the 6 PA-patients, 4 had AST/ALT values slightly elevated at baseline (ranged from 57 to 89 U/l). ALT/AST peak values were above 10x ULN in 2 patients.

Regarding the hepatic AEs reported during all phase II/III studies, 9 PA-patients (0.3 %) experienced hepatobiliary disorders, regardless of causality, compared to 3 patients (0.2 %) in the all comparators-group.

Regarding effect of drug re-administration on transaminases levels, data available remain limited.

Vital signs

In overall phase II/III studies population, no clinically significant mean changes from baseline in systolic or diastolic blood pressure were observed in the 4 treatment groups.

In the all phase II/III studies population, the percentage of subjects with treatment-emergent clinically significant ECG results was highest for the chloroquine-group (2.7 %), followed by the PA-group (1.1 %), the MQ + AS-group (0.7 %) and the AL-group (0.3 %).

The most frequent ECG abnormality was sinus bradycardia in the PA- and AL-groups and prolonged QT_c interval in the MQ + AS- and chloroquine-groups.

Regarding the cardiac AEs reported during all phase II/III studies, 54 PA-patients (1.9 %) experienced cardiac disorders, regardless of causality, compared to 12 patients (1.0 %) in the all comparators-group.

In clinical study, isolated QT_c prolongations, premature ventricular contractions, ventricular extrasystoles and syncope have been observed in clinical phase II/III studies with the use of Pyramax but the signal was not stronger than what was observed in the control groups of comparators used in the studies. Potential for QT interval prolongation was not excluded based on HERG *in vitro* studies.

As already described in the "non-clinical safety pharmacology" section, HERG studies were performed with pyronaridine (P), artesunate and DHA. Those studies showed that artesunate seldom had an effect on hERG tail current up to 300 µM (115.3 µg/mL) and that DHA and pyronaridine both inhibited hERG tail current with IC50s of 282.7 µM and 0.65 µM, respectively. These are equivalent to free plasma levels of 80.37 µg/mL and 591.53 ng/mL (337 ng/mL pyronaridine base), respectively. The applicant states that *in vitro* studies have demonstrated that to achieve such a free plasma concentration, a total blood concentration of 9361.1 ng/mL pyronaridine (P) would be necessary whereas in clinical trials 1180 ng/mL (~ 42 ng/mL free concentration; equivalent to 0.082 µM) have been observed. Such reasoning could stand up if pyronaridine had a restrictive protein binding, which is not established so far, bearing in mind that pyronaridine PK information is insufficient. Also, the compound may as well accumulate in the heart far beyond its free blood concentration. It was pointed out that hERG experiments might have underestimated the value because of an inadequate sensivity assay since remaining tail currents of ~6% are remaining after E4041 challenge. Basically, a "re-run" of this experiment would not further contribute in providing supplementary information, above what can already be extrapolated from the available data.

Indeed,

1. The experiment has been carried out at room temperature which blunts the effects and explains the results
2. Even though the calculation yields tail-currents values >5%, the traces clearly show that E4031 eradicate these tail currents
3. The concentration-effect clearly shows an inhibition of tail currents by pyronaridine (P) and at a lesser level by DHA. A demonstration of a slightly more potent blockade would not add any valuable information.

When observing the Purkinje fibres experiments (study 101202 DCC) that was conducted by the applicant, one can see that at lower concentration, DHA and pyronaridine both increase although modestly, APD durations. Hence there is a slight reverse-use dependency, which confirms potassium channel blockade at low concentrations. However, when increasing the drug concentrations, especially pyronaridine, there is a striking shortening of the APD, which means the drugs profoundly interacts with other channels. Therefore, this study is of little value with regards our concern.

Likewise, the Langendorff study that has been provided is of little use: made with non paced rat hearts, which may barely yield a signal concerning QT prolongation potential, since the models usually used are rabbit or guinea-pig hearts, at fixed paced frequencies.

No thorough QT/QT_c study according to ICH E14 guideline has been performed. From the study 001-03 parts I, II and IV, it appeared that DHA consistently increased the QT_cF (about 5 ms or more) around its T_{max} for C_{max} comprised between 650 to over 1 000 ng/ml.

The QT_c remained however within "acceptable" limits for this class of drugs. QT prolongation is quite a common AE with such drugs but arrhythmias like TdP are exceptional or at least rare enough to be recorded during phase II/III electrocardiographic monitoring, unless continuous. The occurrence of PVCs or monomorphic ventricular extrasystoles in a context of a drug blocking hERG potassium channels is evocative enough to be considered in the ICH E14 list of surrogates of interest linked to I_{Kr} blockade.

In the ritonavir PK study provided (SP-C-010-10), QT_c results cannot be interpreted and no definite conclusions can be drawn. Firstly, contrary to the applicant's statement, ritonavir is known to block IK_r and to possibly induce QT-interval prolongation (see Norvir EU SPC) and therefore cannot be considered similar to placebo. Secondly, surprisingly, while heart rates varied, this variation was only associated to negligible QT-interval variation (taking into account that Friedericia correction also under- and over-corrects QT values, and that is unusual that a drug blocking IK_r, i.e. augmenting the QT interval duration, might induce a QT_c shortening while increasing the heart rate with such correction).

Finally, although ritonavir and Pyramax are susceptible to cause QT-interval prolongation, time-points results showed only negative estimates of the QT_cF.

Safety in special populations

Age

The overall numbers of children in the phase II/III studies exposed to PA is appreciable (< 5 years: 182 patients; 5 – 12 years: 704 patients and 12 – 18 years: 401 patients).

In the PA-group, as well as in the all comparators-group, subjects < 5 years of age had notably higher incidences compared with subjects 5 – 12 years, 12 – 18 years and/or ≥ 18 years of age of the following TEAEs: anaemia and decrease in haemoglobin, vomiting, influenza-like illness, pyrexia, upper respiratory tract infections (including nasopharyngitis and rhinitis), blood albumin decreased, blood glucose decreased, platelet count increased and cough. The incidence of bronchitis was notably greater in the PA-group than in the all comparators group among subjects < 5 years of age (11.5 % vs. 4.2 %).

The incidences of eosinophil count increased (only for the PA-group), anorexia, headache and myalgia were notably higher among subjects ≥ 18 years of age compared with subjects in the younger age categories.

On days 3 and 7, greater percentages of the PA-group compared with the "all comparators" group had potentially clinically significant ALT/AST values, with the difference most notable among subjects ≥ 18 years of age.

Gender

The incidence of PA-patients with neutropenia, vomiting, influenza-like illness, urinary tract infection, blood albumin decreased, blood glucose decreased and platelet count increased was slightly higher in females than males whereas incidences of blood CPK increased, eosinophil count increased and myalgia were slightly higher in male patients than in female patients.

Race

Almost half PA-patients were Asian/Oriental and half patients were Black. More Black PA-patients experienced TEAEs (972/1 426; 68.2 %) than Asian/Oriental patients (639/1 389; 46.0 %).

In the PA-group, lymphocytosis, neutropenia, GI disorders (including abdominal pain, diarrhoea and vomiting), influenza-like illness, pyrexia, bronchitis, rhinitis, upper respiratory infection, urinary tract infection, AST increased, blood albumin decreased, blood glucose decreased, platelet count increased and cough were more frequent in Black patients than in Asian/Oriental patients. On the other hand, eosinophilia/eosinophil count increased, blood CPK increased, anorexia, myalgia, dizziness and headache were more frequently reported in the Asian/Oriental population.

Disease severity factors

No major differences in the incidence of TEAEs by previous malaria episode (yes, no), number of previous malaria episodes in the last 12 months or baseline parasitaemia were observed within the PA-group.

PA doses

Except for ALT on D7 which showed a trend for a dose-relationship (0.5 %, 0.6 %, 0.9 % and 1.5 %), incidences of TEAEs, haematological and biochemistry abnormalities were similar among the PA-subgroups (≤ 8.5:2.8; > 8.5:2.8 to 9.5:3.2; > 9.5:3.2 to 11:3.7 and > 11:3.7).

Other patient subgroups

No data were generated in special populations, such as HIV infected patients or patients with other infections comorbidities and/or comedications as well as patients with a generally impaired health status (e.g. malnutrition).

Safety related to drug-drug interactions and other interactions

There is no information on dosing PA to patients with renal or hepatic impairment and no particular studies have been performed in these populations.

The applicant intends to monitor this risk very closely during post-marketing.

Discontinuation due to adverse events

During the phase II/III clinical programme, the rates of discontinuation due to AEs from study drug or from the study ranged from 0.9 % to 1.3 % and from 0.9 % to 1.6 %, respectively.

In both situations, the most common TEAE leading to discontinuation was vomiting (around 1 %). Although no obvious difference between groups was observed, this may be different in daily practice, or may lead to non compliance and thus treatment failure and should be followed up in a RMP.

Post marketing experience

There was no post-marketing experience for Pyramax at time of application to obtain a scientific opinion.

2.6.1. Discussion on clinical safety

All patients were Asian/Oriental or Black patients, consistent with the claimed use of PA through this Article 58 procedure, to be marketed in endemic area (not in Europe). The majority of patients completed treatment (98.5 % PA, 97.7 % all comparators) and most patients took the planned amount of study drug, consistent with a good compliance during the clinical program. As the dosing ranges have been marginally modified, it is not clear how many patients received dosing in line with the final dose recommendation.

The majority of patients experienced at least one AE. About one quarter of patients experienced AEs considered as drug-related. About one quarter of patients experienced AEs considered as drug-related. The most frequently reported TEAEs for PA patients, regardless causality, were headache (10.6 %), cough (5.9 %), anaemia (4.5 %) and vomiting (4.4 %). In the PA-group, the most frequently affected system organ classes were investigations, blood and lymphatic system disorders, gastrointestinal disorders and nervous system disorders. The most frequent individual DR-AEs for PA patients were headache (3.0 %), eosinophilia (2.5 %) and vomiting (2.2 %).

No death and a low number of SAEs were reported during the clinical program for PA, for which only one was considered as treatment-related. Most discontinuations were due to vomiting in approximately a similar rate for PA and comparators.

The major safety concern is related to cytolytic hepatotoxicity shown by the higher rate of cases of increased ALT/AST in the PA-group than in the comparator treatment groups.

In the cross over designed phase I study SP-C-009-07 (healthy volunteer), 3 cases of increase in alanine aminotransferase (ALT > X 3x ULN and < 10x ULN) were observed for three subjects, after the second dose and was reported as AEs. One of the subjects also showed a concomitant increase in gamma-GT.

The phase II/III trial data do show a relatively high proportion of patients experiencing increase in AST/ALT compared to the reference treatments. During the phase II/III studies, incidences of increased ALT/AST were higher in the PA-group than in the comparator groups. In the PA-group, 93 (3.4 %), 38 (1.4 %) and 11 patients (0.4 %) experienced increase in ALT ≥ 3x ULN, ≥ 5x ULN and ≥ 10x ULN, respectively. A tendency for a dose-relationship for increase in ALT on day 7 emerged.

Some PA-patients and AL-patients had peak ALT ≥ 3x ULN and/or peak AST ≥ 3x ULN and peak total bilirubin ≥ 2x ULN, reaching the definition of the Hy's law. For 3 of them, limited information and/or confounding factors were present but for the 3 remaining cases, a causal relationship could not be formally excluded.

In addition, the percentage of patients in the PA-group who shifted from normal or low baseline value at baseline to high ALT or AST values was greater than in each of the other treatment groups on Days 3 and 7 (PA-group: 9.9 % and 18.7 % for ALAT on Days 3 and 7 respectively and 19.6 % and 20.4 % for AST compared to a range from 4.1 % to 10.5 % for the all comparators-group).

These increases usually occurred on day 3 or 7 and resolved or improved within a month.

Most increases in transaminases remained isolated. Indeed, the patients who experienced ALT ≥ 10x ULN and/or met the Hy's law criteria did not present other AE or reported fatigue, nausea, vomiting, fever, rash as associated AEs.

Besides, only a low number of PA-patients presented hepatic AEs during all phase II/III studies (9 PA-patients (0.3 %) compared to 3 patients (0.2 %) in the all comparators-group).

It should be noted that about 62 % of PA-patients took paracetamol as a concomitant medication (*versus* 66 % for all comparators) but from the available data, there is no obvious interaction between Pyramax and paracetamol on liver function.

Artesunate is not known as a hepatotoxic substance, therefore pyronaridine appears as the suspected compound but the liver toxicity mechanism remains unclear. No mechanistic studies have been provided so far. PA seems to present a cytolytic hepatotoxicity with early onset and rapid resolution but could be potentially serious, especially in case of re-administration over several treatment courses. The preliminary information from the mass balance study provided by the applicant concurs to confirm that the elimination of pyronaridine from the human body will be relatively slow. Redosing experience in human remains limited but there is some evidence of increased liver related adverse events following repeated administration in some healthy volunteers. Although there was a slight trend for higher incidence of raised eosinophils with raised ALTs of up to 3x ULN, no evidence for a concomitant occurrence of increase in transaminases and eosinophils was obvious. No predictable risk factors were identified and at risk patients such as patients with known history or evidence of clinically significant disorders, such as hepatic disorders, jaundice or liver function tests or underlying hepatic morbidity were excluded from all the studies at baseline. No experience on re-administration of treatment courses is available in patients suffering malaria. No data from Chinese pharmacovigilance with pyronaridine was available.

The applicant intends to perform a series of studies to investigate liver toxicity in greater detail, including studies investigating potential hepatotoxic mechanisms and, importantly, repeated dosing studies in healthy volunteers and in patients with *Plasmodium falciparum*. It is the view of the CHMP that information from these studies is essential to determine the full scope of liver toxicity of pyronaridine and the safety of redosing in endemic area.

Regarding cardiac toxicity, it appears from *in vitro* data that both pyronaridine and DHA block potassium channels whilst Pyramax induced isolated prolongation of QT interval and was contemporaneously associated to extra-systoles in patients. The data available from the clinical trials do not show a strong signal though, but are comparable to data obtained for the other antimalarial drugs used as comparators in the comparative clinical trials (mefloquine + artesunate, artemether/lumefantrine, chloroquine). In order to assess the cardiac safety of Pyramax a "thorough QT/QT_c study" according to ICH E14 guideline is advisable (multiple of the therapeutic doses, active comparator, male and female volunteers…). In its absence, caution relevant to this type of risk is expressed in the SmPC.

Cases of potential hypersensitivity, haematological disorders after repeated use with the ACT and the safety profile in patients with haemoglobinopathy will have to be monitored.

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

Additional expert consultations

The advice of an Ad-Hoc Expert Group was sought (9 December 2011) concerning the following safety aspects:

1. **Liver toxicity**

The experts expressed that there is no doubt that Pyramax exhibits an important hepatotoxic potential (via direct toxicity or redox action in liver), observed especially when used over various courses. This clearly limits the repeated use over a short timeframe, in absence of further safeguards.

However, Pyramax could be an important gain to the therapeutic armamentarium in geographic areas of low transmission (low prevalence) with recognised/rapidly emerging ACT resistance, involving resistance to the partner component (amodiaquine, lumefantrine, mefloquine and piperaquine).

An enhanced post-marketing surveillance plan should be in place to collect more data on the liver safety.

The experts also recommended mechanistic studies to get better basic understanding of the hepatoxicity (e.g. exploration of redox status of haem proteins).

The experts also asserted that pyronaridine given as single component (used in China) is known to lead to increases of liver transaminases. However, the experts had no evidence, particularly no high-quality evidence, on either safety or efficacy of monotherapy in China.

2. Safety in special populations.

The experts recommended that in areas where Pyramax would be introduced first, pharmacovigilance would need focus on enhanced post-marketing surveillance in special populations (e.g. patients with HIV/AIDS and severe malnourished patients, pregnant women)

3. Pharmacovigilance & RMP

In that sense, the group expressed that pharmacovigilance activity capability is variable amongst countries/regions. In some countries this would pose difficulties, with unreliable reporting. In other countries however, it is noted that more effective systems are in place. Ideally, there should be active follow-up, with LFT to be obtained in at risk groups, around 3 to 7 days after therapy.

In areas of intended initial marketing of Pyramax (defined areas of SE-Asia), it is more likely that RMP activities can be properly applied.

2.6.2. Conclusions on the clinical safety

In clinical trials, Pyramax, used as single treatment course (3 days) was generally well tolerated. However, the clinical trial data do show a relatively high proportion of patients experiencing increase in AST/ALT compared to the reference treatments. Taking account of potential hepatic accumulation of pyronaridine in liver, to date there are no data to determine the full scope of liver toxicity of pyronaridine and the safety of redosing in endemic area.

In order to assess the cardiac safety of Pyramax a "thorough QT/QT_c study" according to ICH E14 guideline is advisable (multiple of the therapeutic doses, active comparator, male and female volunteers…). In its absence, caution relevant to this type of risk is expressed in the SmPC.

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:

Study SP-C-013-11: A multicenter study to assess the long term safety and efficacy of repeated dose of Pyramax in patients with *Plasmodium falciparum* malaria. To be conducted in Africa. Study initiation had been planned in October 2011 and interim data would be available on December 2012. Mosquito infectivity and feeding trials (including children) after PA treatment will be studied in two sites from this study (methodology of these investigations are in process to be finalised).

Study SP-C-011-10: Phase IIIB (*P. vivax*), randomised, open-label, comparative clinical study to assess the safety and efficacy of a fixed-dose granule formulation of pyronaridine/artesunate (60:20 mg sachet) versus a fixe-dose formulation of artemether/lumefantrine dispersible tablets, in infants and children > 6 months and ≤ 12 years of age (≥ 5 kg and < 25 kg body weight) with acute uncomplicated *Plasmodium vivax* and mixed infections of malaria. This will be conducted in Papua New Guinea (3 sites). The applicant plans to collect PK data in children from this study.

A **pregnancy register** to monitor the outcomes of pregnant treated women in targeted African countries for a first period of 2 years once launched in that region. Registration of pregnant treated women in ongoing registries also to be taken into account.

The applicants states an approach for sentinel adverse event reporting for all ongoing and planned studies, reporting and monitoring of hepatic events and liver biochemistry events including additional investigations in case of confirmed event of interest.

All these measures form part of the RMP.

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

Table 21: Summary of the risk management plan

Safety Concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified		
Increases in liver transaminases	• Information from the repeat dose (SP-C-013-11 and SP-C-014-11) studies • Proactive cohort event monitoring for liver function and adverse events in the initial launch countries with low endemicity and prescribing sites where liver function testing and adverse event reporting is considered feasible and reliable • Routine Pharmacovigilance	• Information in sections 4.1, 4.2, 4.4, 4.8 and 4.9 of the SmPC related to the indication and initial countries for use, single course only and liver function test monitoring and information about ALT rises.
Exacerbation of anaemia	• Information from the repeat dose study (SP-C-013-11) • Routine Pharmacovigilance	• Information in sections 4.4 and 4.8 of the SmPC
Neutropenia	• Information from the repeat dose study (SP-C-013-11) • Routine Pharmacovigilance	• Information in section 4.8 of the SmPC
Vomiting	• Routine pharmacovigilance	• Information in sections 4.2 and 4.4 of the SmPC
Diarrhoea	• Routine pharmacovigilance	
Interaction with medication metabolised through CYP2D6 or via P-gp efflux	• An interaction study with metoprolol (SP-C-014-11) • Routine pharmacovigilance for	• Information in sections 4.5 and 5.2 of the SmPC

Safety Concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	P-gp interactions which are likely to be primarily for the use of digoxin	
Potential		
Use in pregnant and lactating women	To set up a pregnancy register and utilise currently available registries	• Information in sections 4.4, 4.6, 4.6.1 and 5.3 of the SmPC
Neurotoxicity	• Routine pharmacovigilance	• Information in section 5.3
Prolongation of QT and/or bradycardia	• Information from the repeat dose study (SP-C-013-11) • Routine Pharmacovigilance	• Information in Section 4.8
Induction of resistance	• Information from the repeat dose study (SP-C-013-11) • Routine pharmacovigilance	• Information in section 5.1
Tissue accumulation of pyronaridine with inflammation and degenerative changes	• Routine pharmacovigilance	• Information in section 5.3
Skin discolouration	• Routine pharmacovigilance	• Information in section 5.3
Drug interactions with TB or HIV agents metabolised via CYP2D6 pathways	• An interaction study with metoprolol (SP-C-014-11) • Routine pharmacovigilance	• Information in sections 4.5 and 5.2
Missing		
Effect of repeat courses of PYRAMAX	• PYRAMAX will be part of a repeat dose study in which approximately 1344 patients will be or have the potential to be exposed to repeat courses (Annex 5 to RMP). • The repeat dose metoprolol drug interaction study will also provide information ne repeat course of PYRAMAX after 60 or 90 days	• Warnings are provided about the lack of information on repeat dosing are provided in sections 4.2 and 4.4 • Additional warnings about not repeating PYRAMAX, especially if significant rises in liver function tests occur, are provided in section 4.4 • The initial use to be restricted to areas of low transmission is also provided in sections 4.1 and 4.4 • Significant increase in liver transaminases related to the administration of pyronaridine (previously administered) is a contraindication in Section 4.3
Safety in infants	• Information from the repeat dose study (SP-C-013-11) • Information from *P. vivax* study to be planned once safety data from SP-C-011-10 is available	The PYRAMAX SmPC restricts treatment to the tablets which is not indicated for infants
Safety in elderly patients	• Routine pharmacovigilance	Section 4.2 indicates the lack of information and caution in these patients
Severe malnutrition	• Routine pharmacovigilance	
HIV/AIDS infection	• Routine pharmacovigilance	Section 4.2 indicates the lack of information and caution in these patients
Significant anaemia (patients with Hb < 8 g/dL)	• Information from the repeat dose study (SP-C-013-11) • Routine Pharmacovigilance	Information in sections 4.4 and 4.8 of the SmPC

Safety Concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Haemoglobinopathies	• Routine pharmacovigilance	
Patients with hepatic, renal, or cardiac impairment	• Mass balance study (SP-C-012-11) • Routine Pharmacovigilance	• Underlying hepatic injury or significant liver function test abnormalities and severe renal failure will be contraindicated as identified in Sections 4.2 and 4.3 of the SmPC • Caution with regard to moderate renal impairment is provided in Section 4.2, 4.4 and 5.2 • No special precautions are considered to be required for cardiac impairment

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
Repeat dose in patients WANECAM SP-C-013-11 study	Final CSR by 31 March 2016
Repeat dose (and metoprolol interaction) in healthy volunteers SP-C-014-11 study	Final CSR by 30 November 2012
Pregnancy register	Annual updates
Pyronaridine primaquine interaction SP-C-016-11 study	Final CSR by May 2013
Mass balance study (SP-C-012-11)	Final CSR by 30 June 2012

No additional risk minimisation activities were required beyond those included in the product information.

2.8. Significance of paediatric studies

Not applicable

2.9. User consultation

Not applicable

3. Benefit-Risk Balance

Benefits

Beneficial effects

Uncomplicated *P. falciparum* malaria

Beneficial effect was established in the two pivotal studies (Africa, South-East Asia) in patients weighing more than 20 kg.

Both ACT comparators (MQ +AS and AL) used in the pivotal studies (Study SP-C-004-06 and Study SP-C-005-06 respectively) were appropriate as they were the recommended treatments with sustained efficacy in endemic area for uncomplicated *Plasmodium falciparum* malaria at the time the studies were performed.

In comparison with MQ +AS (Study SP-C-004-06), non-inferiority was demonstrated at Day 42 with respect to ACPR (PCR-corrected and crude) based on the (redefined) EE and ITT populations

For the EE population at Day 42 (a total of 18.8% patients excluded as: PA: 17.9%; MQ+AS: 19.8%), the PCR adjusted ACPR was **94.7%** [95%CI: 92.8-96.2] for the PA arm, and 97.1% [95% CI: 94.6%-98.6%] for the MQ+AS arm. The difference between the two treatment groups was **-2.4% [95%CI: -4.7, 0.4].**

For the ITT population at Day 42, the PCR adjusted ACPR was 83.1% [95%CI: 80.4%, 85.6%] for the PA arm, and 83.9% [95% CI: 80.1%, 87.3%] for the MQ+AS arm. The difference between the two treatment groups was **-0.8% [95%CI: -4.9, 3.7].**

In comparison with AL (Study SP-C-005-06), non-inferiority was demonstrated at Day 42 with respect to ACPR (PCR-corrected and crude) based on the EE and ITT populations (see complete efficacy results, discussion, and conclusion above in the Overview).

For the EE population at Day 42 (a total of 15.5% patients excluded as: PA: 15%; AL : 16%), the PCR adjusted ACPR was 91.8% [95%CI: 89.6- 93.7] for the PA arm, and 91.5% [95% CI: 88.2-94.2] for the AL arm. The difference between the two treatment groups was **-0.3% [95%CI: -3.1, 4.1].**

For the ITT population at Day 42, the PCR adjusted ACPR was 83.5% [95%CI: 80.8%, 85.9%] for the PA arm, and 83.0% [95% CI: 79.1-86.4] for the AL arm. The difference between the two treatment groups was **-0.5% [95%CI: -3.7, 5.0].** Median time to parasite clearance was comparable in both treatment groups (approx. 24 hours).

Uncomplicated *P. vivax* malaria

In the treatment of uncomplicated *P. vivax* malaria (Study SP-C-006-06 conducted at sites in Cambodia, India, Indonesia (Maumere), and Thailand) non-inferiority could be demonstrated at Day 28 (with D28 here being considered as the relevant day for the assessment of cure rate) as compared to chloroquine on Crude ACPR in adults and children older than 12 years: cure rate was **88.6%** in the PA group compared to **85.5%** in the chloroquine group (ITT analysis) and **97.1% vs. 98%** respectively for the EE analysis. The difference was **-0.8% [95%CI: -4.3, 2.6]** in the EE population and **3.1% [95%CI: -3.1, 9.3]** in the ITT population. Time to parasite clearance was significantly shorter in the PA group as compared to the chloroquine group (median time: 23.1 and 32.0 hours in the PA and chloroquine groups, respectively).

Uncertainty in the knowledge about the beneficial effects

No clinical studies included Central or South American sites.

Pharmacokinetics

No complete data are submitted to cover and support the absorption, distribution, metabolism and elimination of pyronaridine.

Pharmacokinetics in paediatric population (less than 20 kg body weight) is not adequately documented and therefore is not part of the granted indication.

Effect against drug resistant *Plasmodium falciparum:*

Noticeable results in Cambodia site:

In the Cambodia site (Pailin), a higher rate of recrudescences was observed in the PA treated group as compared to the MQ+AS treated group and as compared to the other areas included in the study SP-C-004-06 (conducted from January 2007 to October 2008). Also, consistently with the emerging reduced susceptibility to artemisins that has been reported in Cambodia-Thailand border region (ref: Noedl H, N Engl J Med 2008; Dondorp AM, N engl J Med 2009), slower parasite clearance time was observed at this site as compared to the other countries of the study. No other phase III study is available at Cambodia sites.

Based on the available results in this multiple drug resistant country, pyronaridine did not show to provide any benefit as compared to mefloquine with respect to recrudescences rate.

The ad-hoc experts group remarked that in this country *P. falciparum* resistance is very fluent and dynamic and as mefloquine resistance locally reappeared and increased since 2006, it cannot be excluded that the rate of recrudescences with MQ+AS combination could be higher now than what was observed in the study SP-C-004-06 conducted between 2007 and 2008, leading to probable different results between the compared groups. This suggestion could be endorsed but it cannot be excluded that pyronaridine resistance status/recrudescences could have evolved/increased too. No comparative data are available in the current context of endemic resistance.

Plasmodium vivax malaria

The *P. vivax* studies (SP-C-006-06 and SP-C-008-07) included a majority of adults excluding patients with severe anaemia (i.e. haemoglobin < 8 g/dl). Only 13 PA (vs. 15 CQ) children from 7 to 12 years old were studied. No patients below the age of 7 years were included. Data remain sparse in the paediatric most vulnerable population prone to severe outcomes with *Plasmodium vivax*.

Moreover, no data are available with Pyramax in areas where chloroquine-resistance of *Plasmodium vivax* has been described as a real concern i.e. mostly in Northeastern Papua, close to the border between Indonesia and Papua New Guinea (according to WHO 2010).

According to the Ad hoc experts group advice, *Plasmodium vivax* malaria efficacy/safety results observed from study SP-C-006-06 can be extended to children more than 20 kg body weight as no difference would be expected on PK and safety grounds and with respect to acquired immunity in endemic area in the paediatric population more than 20 kg body weight as compared to the characteristic of the largest part of the population that was included in the malaria trial.

Further data are expected in young children in Papua New Guinea (high level of resistance of *P. vivax* to chloroquine) that will better target the at risk population to address the potential benefit of Pyramax in *Plasmodium vivax* malaria in endemic area.

In the meantime, the information on the origin of presently available data in *P. vivax* malaria has been clarified in section 5.1 of the SmPC, also mentioning the demographic characteristics (only 13PA children vs. 15 CQ less than 12 years and no children less than 7 years included). Also it has been clarified that the study was conducted in area of low resistance to chloroquine.

Efficacy and safety in children 15 – 20 kg:

Based on the available data, the safety/efficacy ratio is not established in children 15- 20 kg as initially claimed by the applicant.

Therefore, the indication of PA tablets is restricted to patients with body weight > 20 kg.

The applicant has planned to further investigate children (*Plasmodium vivax* malaria study) and concomitantly to develop a granule formulation as it is a more suitable presentation for paediatric dosing in the youngest children.

Gametocytes carriage:

The gametocytes clearance time consistently appeared longer in the PA groups as compared to MQ+AS or AL in all studies conducted in *Plasmodium falciparum* malaria. These observations could be worrying with regard to transmission with particular concerns in area with emerging lower sensitivity of *P. falciparum* to artesunate and ACT resistance (e.g. Cambodia-Thaïland border region). The applicant plans to perform further comparative trials assessing the viability of the gametocytes and mosquito infectivity after PA treatment (including membrane feeding).

In this respect, a proper wording has been introduced in section 5.1. of the SmPC.

HIV/AIDS/ malnourished population:

No information in patients with underlying co-morbidities, as HIV-infections/AIDS as well as patients with a general impaired health status (e.g. malnutrition) or co-medications.

The applicant intends to perform enhanced monitoring of adverse effects in these populations with special reporting and follow-up in the PSURs.

Pregnancy:

No data are available in pregnant women while they are part of the identified at risk population.

The applicant plans a pregnancy register to monitor the outcomes of pregnant treated women in African countries for a first period of 2 years once launched in this region. Registration of pregnant treated women in on going registries is also planned and within the framework of Cohort Event Monitoring (CEM) in the South-East Asia.

Drug-drug interactions

Further data are needed with regard drug-drug interactions. The applicant intends to conduct two interaction studies with primaquine and with metoprolol (as CYP2D6 substrate).

Risks

Unfavourable effects

Over 25% of patients receiving PA experienced a treatment related adverse event. The most common treatment related adverse events were headache (3.0% in the PA group) followed by eosinophilia (2.5%), vomiting (2.2%), neutropenia (1.9%), AST increased (1.7%) and anaemia (1.6%).

The major safety concern is related to cytolytic hepatotoxicity shown by the higher rate of cases of increased ALT/AST in the group of patients treated with a 3 days course of PA treatment as compared to the other comparators:

Pyramax: ALT ≥ 3x ULN = 93 (3.4%); ≥ 5x ULN = 18 (1.4%); ≥ 10x ULN = 11 (0.4%); 0.1% were potential Hy's law cases.

All comparators (AL, MQ+AS): ALT ≥ 3x ULN = 7 (0.6%); ≥ 5x ULN = 3 (0.2%); ≥ 10x ULN = 1(0.1%);

No fatal case was reported.

Uncertainty in the knowledge about the unfavourable effects

Liver toxicity and re-treatment with Pyramax:

The mechanism of liver toxicity is not established and no experience is available in case of re-treatment with Pyramax.

There is evidence of potential cytolytic hepatoxicity with a single 3-day course of Pyramax as observed in clinical phase II/III studies, and there is indication of increased liver transaminases following repeated administration of single dose of pyronaridine:artesunate 720:240 mg after 43 days wash out in healthy volunteers.

No data on repeated 3-days treatment course with Pyramax in malaria is presently available.

Moreover, as liver function test abnormality was an exclusion criterion of the clinical phase III studies, no clinical experience is available in patients with underlying liver injury receiving with Pyramax.

As artesunate is not known as a hepatotoxic substance, pyronaridine appears as the suspected drug with respect to the Pyramax liver toxicity issue. No pharmacovigilance data from China, where pyronaridine has been used for several years, has been obtained. However, according to the ad- hoc expert group, pyronaridine used as monotherapy was already known to lead to increases of liver transaminases.

The mechanism of liver toxicity of pyronaridine has not been established so far. The applicant is planning a series of studies to investigate possible mechanisms, and to evaluate the safety/risk of repeated use both in healthy volunteers as well as in malaria patients.

Cardiac toxicity:

Regarding cardiac toxicity, no strong signal arose from the available phase III clinical studies as compared to the other antimalarial medicinal products (artemether/lumefantrine, mefloquine + artesunate, chloroquine). However, as it was shown from *in vitro* data that both pyronaridine and DHA block potassium channels and as Pyramax induced isolated prolongation of QT interval and was contemporaneously associated with extra-systoles in clinical studies, a warning is included in section 4.4 and further information is provided in sections 4.5, 4.8 and 5.1 of SmPC.

Benefit-risk balance

On current evidence, the risk-benefit balance of Pyramax in treatment of acute uncomplicated malaria infections caused by *P. falciparum* or *P. vivax* in adults and children weighing 20 kg and more could be deemed favourable for a limited indication only. It should be restricted to single (3-day) treatment

course only (in any given patient). This position takes into account the risk for severe hepatic side effects which might possibly result from repeated use of Pyramax.

The benefit/risk of using Pyramax is to be acceptable only under following strict conditions:

- one single 3-days treatment course only (not to be repeated in any given patient).
- should only be dispensed at facilities equipped to undertake the required liver function monitoring
- only in areas with low malaria transmission and with evidence of resistance to artemisinin combination treatments (ACTs), consistent with World Health Organisation's (WHO) recommendations for artemisinin resistance.

Further data are requested before the CHMP would consider whether those recommendations can be altered. CHMP is of the opinion that information from the planned studies is essential to determine the full scope of liver toxicity of pyronaridine and the safety of redosing in endemic area.

Discussion on the benefit-risk balance

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes and affects mainly young children and pregnant women. The WHO estimates that in 2010, there were 216 million cases of malaria with some 655 000 deaths.

Malaria is curable and preventable, with principal control strategies including rapid diagnosis, effective treatment and personal protection with bed nets. Currently a number of antimalarials are available. However, *P. falciparum*, the parasite causing the most lethal type of human malaria, has become resistant to many conventional treatments in most parts of the world. Artemisinin derivatives, including artesunate, are widely used anti-malarial drugs, clearing parasites rapidly. Resistant strains of *P. falciparum* might develop if artemisinin derivatives are used alone. In order to prevent the occurrence of drug resistance to artemisinins and to address the issue of its relatively short half-life, artemisinins are recommended by the WHO to be given in combination with another anti-malarial agent with a longer half-life.

In the case of Pyramax, the artemisin derivative (artesunate) has been combined with pyronaridine tetraphosphate.

Acceptable efficacy results (non-inferior to comparator) were obtained in the provided pivotal studies, for this new combination assessed in the treatment of acute uncomplicated malaria infection caused by *P. falciparum* or by *P. vivax* in subjects more than 20 kg body weight.

The adverse events profile for Pyramax has been established in clinical trials (phase II to III studies) in approximately 2800 patients. Pyramax was generally well tolerated.

However, there is evidence of potential hepatoxicity with a single 3-day course of Pyramax as observed in clinical phase II/III studies, and there is indication of increased liver transaminases following repeated administration of single dose of pyronaridine:artesunate 720:240 mg after 43 days wash out in healthy volunteers.

Artesunate has not been reported to relate to liver toxicity and pyronaridine appears as the responsible substance of the liver toxicity of this new ACT. The mechanism of liver toxicity has not been established so far.

Due to concerns about severe liver problems associated with repeated use, the CHMP, after taking advice from the Ad-Hoc Expert Group, considered that the risk-benefit balance of Pyramax is

favourable only if used as a single 3-day treatment course. It is proposed that Pyramax be dispensed at facilities equipped to undertake the required liver function monitoring and only in areas with low malaria transmission and with evidence of resistance to artemisinin combination treatments (ACTs), consistent with World Health Organisation's (WHO) recommendations for artemisinin resistance.

The applicant should however further investigate possible mechanisms of liver toxicity (Recommendation) and perform repeated dosing studies (RMP measure) to determine the full scope of hepatotoxicity of Pyramax and the safety of repeated treatment courses in endemic areas. These data will allow the CHMP to consider whether the current SmPC conditions/restrictions can be altered.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Pyramax in the treatment of

"acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in adults and children weighing 20 kg or more, in areas of low transmission with evidence of artemisinin resistance. Pyramax is to be used only as a single treatment course in any given patient (see section 4.2 and 4.4.)

Consideration should be given to official guidance on the appropriate use of antimalarial agents (see section 4.4)"

is favourable. This opinion is based upon the risk-benefit scenarios on the populations and conditions of use as documented with clinical data by the applicant.

This medicinal product, Pyramax 180mg/60mg film-coated tablet, is exclusively intended for markets outside the European Union.

Recommendations regarding supply and use

Medicinal product subject to medical prescription

Other recommendations and requirements of the Scientific Opinion Holder

Pharmacovigilance system

The Scientific Opinion Holder must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Scientific Opinion Application is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The Scientific Opinion Holder shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in the Risk Management Plan presented in Module 1.8.2. of the Scientific Opinion Application and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (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 European Medicines Agency.

PSURs

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