# APPLICATION FOR INCLUSION OF

# PYRONARIDINE TETRAPHOSPHATE / ARTESUNATE FIXED DOSE COMBINATION TABLETS AND GRANULES

# IN THE WHO MODEL LISTS OF ESSENTIAL MEDICINES

## TABLE OF CONTENT

**1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION ..... 5**
Rationale on the proposed formulation: ..... 6
Rationale on the proposed dosage form: ..... 6
Dosage: ..... 7
PHARMACEUTICAL DEVELOPMENT ..... 8
Proof of efficacy and safety: ..... 8
Overall comparative efficacy of pyronaridine /artesunate tablets and granules: 8
Overall comparative safety of pyronaridine /artesunate tablets and granules: ... 8
Rationale on cost: ..... 9
Quality: ..... 9

**2. NAME OF THE FOCAL POINT IN WHO SUBMITTING OR SUPPORTING THE APPLICATION ..... 10**

**3. NAME OF THE ORGANISATION(S) CONSULTED AND/OR SUPPORTING THE APPLICATION ..... 11**

**4. INTERNATIONAL NON-PROPRIETARY NAME (INN, GENERIC NAME) OF THE MEDICINE ..... 12**

**5. DOSAGE FORM OR STRENGTH PROPOSED FOR INCLUSION ..... 13**
5.1 Chemical characteristics ..... 13
5.2 The formulation proposed for inclusion: ..... 13
5.2.1 Summary of Efficacy ..... 14
5.2.2 Summary of Safety ..... 15
5.2.3 Posology ..... 16
5.3 Stability of the formulations ..... 17

**6. INTERNATIONAL AVAILABILITY – SOURCES, IF POSSIBLE MANUFACTURERS ..... 18**
6.1 Sources and manufacturers ..... 18
6.2 History of the product ..... 18
6.2.1 Background on artemisinin-based combinations (ACTs) ..... 18
6.2.2 Rationale for Development ..... 19
6.3 International availability and production capacity ..... 20

**7. WHETHER LISTING IS REQUESTED AS AN INDIVIDUAL MEDICINE OR AS AN EXAMPLE OF A GROUP ..... 22**

**8. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE (EPIDEMIOLOGICAL INFORMATION ON DISEASE BURDEN, ASSESSMENT OF CURRENT USE, TARGET POPULATION) ..... 23**
TARGET POPULATION AND RATIONALE ON THE RATIO/DOSE ..... 24

**9. TREATMENT DETAILS ..... 27**
9.1 Method of administration ..... 27

9.2 Dosage ..... 27
9.3 Duration ..... 28
**10. SUMMARY OF COMPARATIVE EFFECTIVENESS IN A VARIETY OF CLINICAL SETTINGS ..... 29**
Phase II Paediatric Study of pyronaridine /artesunate ..... 32
Overall conclusion from phase II studies ..... 36
Phase III studies with pyronaridine /artesunate ..... 36
Conclusions on the overall comparative efficacy of pyronaridine / artesunate tablets and granules ..... 53
**11. SUMMARY OF COMPARATIVE EVIDENCE ON SAFETY ..... 54**
11.1 Safety and tolerability ..... 54
Overview of Safety ..... 54
Conclusions on Safety from Phase II/III ..... 56
11.2 A Risk Management Plan for pyronaridine artesunate fixed-dose combination ..... 57
11.3 Use in pregnancy and lactation ..... 57
11.4 Drug interactions ..... 58
**12. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST - EFFECTIVENESS WITHIN THE PHARMACOLOGICAL CLASS OR THERAPEUTIC GROUP ..... 59**
**13. SUMMARY OF REGULATORY STATUS OF THE MEDICINE (IN COUNTRY OF ORIGIN, AND PREFERABLY IN OTHER COUNTRIES AS WELL) ..... 60**
**14. AVAILABILITY OF PHARMACEUTICAL STANDARDS ..... 61**
**15. PROPOSED TEXT FOR THE WHO MODEL FORMULARY ..... 62**
15.1 NAME OF THE MEDICINAL PRODUCT ..... 62
15.2 QUALITATIVE AND QUANTITATIVE COMPOSITION ..... 62
15.3 PHARMACEUTICAL FORM ..... 62
15.4 Clinical particulars ..... 62
15.4.1 Therapeutic indications ..... 62
15.4.2 Posology and method of administration ..... 63
15.4.3 Contraindications ..... 64
15.4.4 Special warnings and precautions for use ..... 64
15.4.5 Interaction with other medicinal products and other forms of interaction 65
15.4.6 Fertility, pregnancy and lactation ..... 65
15.4.7 Undesirable effects ..... 66
15.4.8 Overdose ..... 68
15.5 PHARMACOLOGICAL PROPERTIES ..... 68
15.5.1 Pharmacodynamic properties ..... 68
15.5.2 Pharmacokinetic properties ..... 70
15.5.3 Preclinical safety data ..... 72

15.4 Shelf life ..... 74
15.5 Special precautions for storage ..... 74
15.6 Nature and contents of container ..... 74

# 1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION

Malaria is a parasitic disease that threatens half of the world's population. In 2006, the World Health Organization (WHO) reported 247 million cases out of the estimated 3.3 billion people at risk of the disease. In the same year, malaria caused nearly one million deaths; 91% of the mortality was in Africa with children less than 5 years of age attributing 85% of deaths (WHO, 2008). While global efforts have led to the significant progress in the prevention, diagnosis, and management of malaria, treatment of malarial infections in the face of emerging drug resistance among *Plasmodium sp*. continues to pose clinical challenges. In particular, the widespread resistance of *Plasmodium falciparum* has rendered conventional monotherapies such as chloroquine, amodiaquine, sulfadoxine/pyrimethamine (S/P) ineffective.

Artemisinins and its derivatives are currently the most potent and rapidly acting antimalarial agents available to date (Ashley 2005). Their antimalarial activities are characterized with high parasite kill rates and broad-stage activity thereby producing faster clinical and parasitological response than other classes of antimalarial agents. Their peroxidic pharmacophore is believed to be the main source of its potent activity. However, artemisinins have been associated with high recrudescence rates when used as monotherapy if given using the conventional 3-5 days of therapy (Bunnag 1991). To combat increasing levels of resistance, the WHO currently recommends artemisinin-based combination therapy (ACT) as the first-line therapy in areas with high prevalence of resistance (RBM 2006). Its combination with other agents has allowed for shorter courses of ACT therapy, improved treatment outcomes and enhanced patient compliance.

The WHO recommends that combinations of antimalarials should be used to counter the threat of resistance to *P.falciparum* monotherapies and to improve treatment outcomes. Combinations of artemisinin derivatives with other agents (Artemisinin based Combination Therapy, ACT) are recommended for frontline treatment of uncomplicated *P.falciparum* malaria, and also for uncomplicated *P. vivax* (*WHO, 2006a, WHO 2006b*).

The combination of pyronaridine tetraphosphate (PP) and artesunate (AS), as a new ACT, has been developed to fulfil these needs. PYRAMAX is the name given to the 3:1 combination of pyronaridine tetraphosphate and artesunate as a co-formulated combination product.

Shin Poong Pharmaceutical Co., Ltd is a pharmaceutical company established in Seoul, South Korea since 1962 that develops and manufactures medicines in their own facilities and markets them in many regions. . Shin Poong is the sponsor of the Article 58 application proposed for *PYRAMAX*. The development has been undertaken in partnership with the Medicines for Malaria Venture (MMV), a not-for-profit foundation based in Geneva, Switzerland. The programme has been managed by a drug

development team which has received input from a wide range of experts including MMV's Expert Scientific Advisory Committee, the World Health Organization (WHO) Roll Back Malaria Partnership and Global Malaria Programme, as well as malaria specialists from Africa and South East Asia.

Shin Poong has manufactured the *PYRAMAX* 3:1 combination product for clinical studies and future commercial use at their GMP compliant facilities in South Korea. Preclinical studies have been performed to ICH standards with the individual active substances and with the combination as appropriate. Clinical studies at phases I, II and III have been completed with the tablet and granule formulations. The Company holds a New Drug Application (K-NDA) for *PYRAMAX* from the Korean regulatory agency during 2010.

***Rationale on the proposed formulation:***

The goal of anti-malarial drug development is to develop potent, safe, easy-to-administer, and inexpensive combination therapies. There is a need for new drugs that are efficacious against both *P. falciparum* and blood stage of *P. vivax*, because in areas where both species exist and health systems are undersourced, it is often not possible to distinguish between the 2 species at the initial diagnosis. Given the data accumulated to date, it is anticipated that the combination of pyronaridine tetraphosphate and artesunate as a fixed dose ACT, will fulfil these needs.

*PYRAMAX* is an immediate release film coated tablet containing 60 mg of artesunate and 180 mg of pyronaridine tetraphosphate presented in tablet and 20 mg of artesunate and 60 mg of pyronaridine tetraphosphate presented in granule formulation.

The following are the key features of *PYRAMAX*

- **Once a Day - for 3 Days**
- **Label indication for both *P falciparum* and blood stage *P vivax* infections**
- **Simple dosage and regimen - better cure effect**
- **Weight neutral package resulting in less stock out**

***Rationale on the proposed dosage form:***

Since the outbreak areas for malaria are mainly the underdeveloped regions of the world such as Africa any new dosage form of anti-malarial medicine should be designed to achieve better patient compliance. Thus, the oral route of drug administration was preferred and tablets and granules were considered to be convenient for the patients.

**The single strength of pyronaridine /artesunate *PYRAMA*X TABLET contains 180 mg pyronaridine tetraphosphate and 60 mg artesunate.**

**The single strength of pyronaridine /artesunate *PYRAMA*X GRANULES contains 60 mg pyronaridine tetraphosphate and 20 mg artesunate.**

The dose should be taken orally once a day for three days.

Pyronaridine /artesunate tablets and granules 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:***

***TABLETS***

*Dosage in adults and children*

Pyronaridine /artesunate tablets should be taken orally as a single daily dose for three consecutive days.

| Body weight | Number of tablets | 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 |

***GRANULES***

*Dosage in children and infants*

Pyronaridine /artesunate granules should be taken orally as a single daily dose for three consecutive days.

| Body weight | Number of granule sachets | Regimen |
|---|---|---|
| 5 - < 8 kg | 1 sachet | Daily for 3 days |
| 8 - < 15 kg | 2 sachets | Daily for 3 days |
| 15 - < 20 kg | 3 sachets | Daily for 3 days |
| 20 - < 25 kg | 4 sachets | Daily for 3 days |

## *PHARMACEUTICAL DEVELOPMENT*

**Pyramax contains:**

- The active substances of pyronaridine tetraphosphate and artesunate.
- Other ingredients of microcrystalline cellulose, crospovidone, mannitol (E421), magnesium, stearate, talc, hypromellose, macrogol, hypromellose, titanium dioxide, tartrazine (E102), sunset yellow FCF (E110).

Pyronaridine/artesunate are antimalarial agents with a history of clinical use both separately and in combination with other drugs. Each drug has powerful schizonticidal actions but the combination of the two is expected to show pharmacological addition in man. The action of artesunate is a rapid knock-down of the parasites, after which the drug is rapidly cleared as it has a short systemic half-life. Pyronaridine is also effective in the short-term but has an intermediate blood half-life thus providing a sustained schizonticidal effect. The aim of the fixed dose combination of pyronaridine/artesunate in the treatment of uncomplicated acute malaria is to provide a rapid reduction in parasitaemia with a three-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

### *Proof of efficacy and safety:*

***Overall comparative efficacy of pyronaridine /artesunate tablets and granules:***

From the Phase III studies, pyronaridine /artesunate fixed combination was shown to have good efficacy, safety and tolerability profiles in children and adults patients for the treatment of acute, uncomplicated *P. falciparum* or *P. vivax* malaria in Africa and South East Asia.

Pyronaridine /artesunate was shown to be at least as effective as mefloquine+artesunate and artemether lumefantrine (for both tablet and granule formulations) for the treatment of patients with acute, uncomplicated *P. falciparum* malaria and also at least as effective as chloroquine for the treatment of subjects with acute *P. vivax* malaria.

The comparative studies consistently demonstrated greater efficacy rate compared to the 2006 WHO limit of 95% of PCR corrected ACPR level.

***Overall comparative safety of pyronaridine /artesunate tablets and granules:***

Approximately 3000 subjects received pyronaridine /artesunate across the completed Phase I, Phase II, and Phase III studies.

Safety was assessed in these studies by physical examinations, adverse events, vital signs, laboratory assessments (haematology, biochemistry, urinalysis), clinical signs and symptoms, and 12-lead electrocardiogram (ECG). The main adverse events observed in

the pyronaridine /artesunate group included headache, cough, abdominal pain, vomiting and nausea. Vomiting was the most common adverse events leading to study drug discontinuation and withdrawal from the studies.

***Rationale on cost:***

In public sectors, Global prices of various different ACTs show stable behaviour in terms of price movement since the launching of AMFm. Strong buyer's power has made different ACT price on minimum level while key raw material artemisinin price moves from U$200 up to U$600/Kg. For the price fluctuation of artemisinin, manufacturers take the price volatility while keeping the price of ACT as low as they can manage.

Under this situation, pyronaridine/artesunate price should follow global price trend in order to keep the product competitive in different dimension of the market place. Therefore, the price will be;

- Tablet pyronaridine 180mg/artesunate 60mg price will be U$0.545 – 2.18 per treatment in different weight band excluding delivery, cargo insurance and tax from country of origin in public sectors.
- Granule pyronaridine 60mg/artesunate 20mg price will be U$0.252 -1.008 per treatment in different body weight excluding delivery, cargo insurance and tax from country of origin in public sectors

***Quality:***

Pyronaridine/artesunate fixed dose combination tablets and granules are manufactured by:

Shin Poong Pharmaceutical Co., Ltd
408-4, Moknae-Dong, Ansan-Si,
Kyunggi-Do
Korea

This facility has been constructed and equipped in line with EU Good Manufacturing Practice (GMP) and will have been Inspected by the European Medicines Agency (EMA) January 2011 as part of the review of the Article 58 Submission for Opinion Status. Inspection by WHO prequalification inspection is pending. Sufficient quantities of tablet and granules are to be manufactured to meet expected needs.

Both pyronaridine tetraphosphate and artesunate are manufactured at the same site as the tablet and granule formulations. Active ingredients are GMP compliant.

## 2. NAME OF THE FOCAL POINT IN WHO SUBMITTING OR SUPPORTING THE APPLICATION

Not applicable

# 3. NAME OF THE ORGANISATION(S) CONSULTED AND/OR SUPPORTING THE APPLICATION

MMV: Medicines for Malaria Venture
International Center Cointrin (ICC) Building
20, route de Pré-Bois
CH-1215 Geneva 15- Switzerland

# 4. INTERNATIONAL NON-PROPRIETARY NAME (INN, GENERIC NAME) OF THE MEDICINE

Pyronaridine /artesunate tablet and granules are a fixed dose combination of two antimalarial drugs pyronaridine (INN) and artesunate (INN).

# 5. DOSAGE FORM OR STRENGTH PROPOSED FOR INCLUSION

## 5.1 Chemical characteristics

Pyronaridine is a benzonaphthyridine derivative first synthesized in 1970 at the Institute of Chinese Parasitic Disease, Chinese Academy of Preventative Medicine (Zheng et al., 1982; Zheng et al., 1979; Chen & Zheng, 1992). The pyronaridine nucleus is based on mepacrine (a 9-aminoacridine) with the addition of an amodiaquine-like side chain (Chang et al., 1992; Chen & Fleckenstein, 2001). The drug is formulated as pyronaridine tetraphosphate, a yellow, odourless powder with a bitter taste (Chang et al., 1992). As the use of pyronaridine for the treatment of malaria has been limited to China over the last 30 years, it is expected that resistance will be slow to develop across other malarial regions of the world.

Artemisinin is an antimalarial drug consisting of a sesquiterpene lactone ring with a unique endoperoxide dioxygen bridge in which the antimalarial activity resides. Extracts of artemisinin or 'qinghaosu' have been utilised for hundreds of years as antipyretic herbal remedies in China. However, it was not until 1971 that the antimalarial property of artemisinin was described (Anon, Qinghaosu antimalarial co-ordinating group, 1979). Artemisinin is readily purified from *Artemisia annua* (sweet wormwood) and has been used to treat malaria in China since the early 1970's (Meshnick et al., 1996; Van Agtmael et al.; 1999; Price, 2000). Since this initial discovery a number of semi synthetic oil and water soluble derivatives of artemisinin have been developed with a variety of formulations entering clinical studies. *In vivo*, artemisinin and its derivatives are rapidly converted to dihydroartemisinin (DHA), the active metabolite.

Artesunate is the most widely used member of the artemisinin derivative drugs. It is effective against strains of *P. falciparum* resistant to all other antimalarial drugs in common clinical practice, as well as *P. vivax*.

Pyronaridine tetraphosphate is a blood schizonticide antimalarial therapy synthesised in China in 1970. Available data indicate that pyronaridine is effective in cases of chloroquine resistance and seems to be satisfactorily tolerated (Zheng *et al*, 1982). Pyronaridine (oral and injectable formulations) is currently marketed in China under the trade name Malaridine and was administered in combination with other agents with the aim of preventing the appearance of drug resistance (Ringwald *et al*, 1999, Chen and Zheng, 1992). The physicochemical properties of pyronaridine have been recently determined (Olajire *et al,* 2006).

## 5.2 The formulation proposed for inclusion:

Pyronaridine/artesunate are antimalarial agents with a history of clinical use both separately and in combination with other drugs. Each drug has powerful schizonticidal actions but the combination of the two is expected to show pharmacological addition in

man. The action of artesunate is a rapid knock-down of the parasites, after which the drug is rapidly cleared as it has a short systemic half-life. Pyronaridine is also effective in the short-term but has an intermediate blood half-life thus providing a sustained schizonticidal effect. The aim of the fixed dose combination of pyronaridine/artesunate in the treatment of uncomplicated acute malaria is to provide a rapid reduction in parasitaemia with a three-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

Based on existing clinical data and clinical practice, the ratio of pyronaridine to artesunate of 3:1 w/w has been developed. Doses have been selected to be in line with current prescribing practice for the agents when used as monotherapy. The drug development programme for PYRAMAX has been designed to meet a target product profile for curative treatment of a once daily administration of a fixed dose tablet formulation pyronaridine/artesunate, for 3 days to patients with acute *uncomplicated P. falciparum* and blood stage *P. vivax* malaria.

A full package of regulatory compliant pre-clinical studies on pyronaridine/artesunate alone and in combination, has been conducted to GLP standards. The drug materials have been produced to GMP standard by the Sponsor, Shin Poong Pharmaceutical Co., Ltd (SPP). The combination product has been developed by SPP in conjunction with Medicines for Malaria Venture (MMV) as a public private partnership.

### *5.2.1 Summary of Efficacy*

In the phase II adult and the paediatric trials, 28-day PCR corrected ACPR as well as parasite clearance time showed promising efficacy for the fixed dose combination of pyronaridine /artesunate.

In the phase III studies, the pyronaridine /artesunate fixed combination was shown to be at least as effective in cure rate as mefloquine (MQ) + artesunate (AS) and artemether lumefantrine (AL) (for both tablet and granule formulations) for the treatment of patients with acute, uncomplicated *P. falciparum* malaria and also at least as effective as chloroquine for the treatment of subjects with acute *P. vivax* malaria. The parasitological re-appearance (new infection or recrudescence) rate was statistically significantly lower with pyronaridine /artesunate compared with MQ + AS at Day 42. In addition, the parasitological re-appearance rate on Day 28 was statistically significantly lower with pyronaridine /artesunate compared with MQ + AS for the ITT population. Rates of new infection or parasitological re-appearance were statistically significantly lower with pyronaridine /artesunate compared with AL through Day 28 and Day 42 (ITT). In *P. vivax* patients, the risk of infection with *P. falciparum* was statistically significantly lower with pyronaridine /artesunate than with chloroquine based on ITT population. For the paediatric granule formulation no statistically significant difference between the pyronaridine /artesunate and AL groups was observed for the Kaplan-Meier estimates of new infection or recrudescence, as determined by PCR analysis on the ITT population.

Time to parasite clearance was similar in pyronaridine /artesunate and MQ + AS treatment group. One notable finding was that, for western Cambodia, parasite clearance time was almost 2-fold longer than for the other sites in this study reflecting a potential change in sensitivity to artesunate in this geographical area. However time to parasite clearance was statistically significantly shorter in the pyronaridine /artesunate group compared with the AL and CQ groups. Time to fever clearance was similar in the pyronaridine / artesunate, MQ + AS and AL groups. However pyronaridine /artesunate was significantly faster at clearing fever than CQ.

### *5.2.2 Summary of Safety*

From the literature, the profile of adverse events of pyronaridine or artesunate includes abdominal pain and appetite perturbation that may result from pyronaridine therapy and possibly from artesunate. CNS-related events and QT interval prolongation have been reported in up to 1% of patients in a single review of artemisinin derivatives but no such changes were evident with the present combination, whether in the animal studies or in clinical trials, either with pyronaridine or artesunate alone or in combination. Occasional neutropenia, reticulocytopenia and elevated liver enzymes were reported, as well as dizziness, nausea, vomiting and diarrhoea reported in a series of patients treated with artesunate or artemether. Adverse events associated with artesunate treatment are transient in nature. At a total dose level of 12 mg/kg artesunate was well tolerated with no evidence of attributable CNS-related, ECG changes or allergic reactions. Since acute malaria is associated with symptoms of lassitude, nausea, vomiting, abdominal pain, dizziness, headache, muscle pain, and sometimes diarrhoea, it is often difficult in the acute phase of the disease to distinguish disease effects from drug effects (Price *et al*, 1999). In none of the reviews were serious adverse events associated with therapy from pyronaridine or artesunate other than anecdotal reports of allergic reaction.

The profile of adverse events in patients has been established for pyronaridine / artesunate in clinical trials (phase I to III studies) in approximately 2925 adults and children suffering from uncomplicated malaria with an age range of 3 months to 60 years of age.

The adverse event profile of pyronaridine /artesunate was consistent with those reported for pyronaridine and artemisinins as monotherapy. Treatment-emergent adverse events reported for ≥5.0% of subjects in any study were headache (10.6%) and cough (5.9%). Most adverse events are expected to be of mild or moderate nature and to resolve spontaneously. In some cases it may be difficult to distinguish adverse events such as vomiting, headache and fever from malarial symptoms. The most common treatment-emergent adverse events leading to study drug discontinuation in each study was vomiting.

Pyronaridine / artesunate was well tolerated in all age group: no notable differences in incidence of treatment-emergent adverse events were observed by age group. However subjects below 5 years age had notably higher incidences compared with subjects 5-12

years, >12-<18 years, and/or ≥18 years of age of the following treatment-emergent adverse events: anaemia, vomiting, influenza like illness, pyrexia, bronchitis, upper respiratory tract infection, blood glucose decreased, platelet count increased, and cough. The incidences of headache and myalgia were notably higher among subjects ≥18 years of age compared with subjects in the younger age categories. Also the incidence of bronchitis was notably greater in the pyronaridine /artesunate group than in the all comparators group among subjects <5 years of age (11.5% vs. 4.2%).

Pyronaridine /artesunate treatment was associated with transient ALT elevations in a small subset of subjects. The early onset (Day 3-7) and rapid resolution are consistent with a direct, low-level toxicity and do not indicate a risk of progressive liver injury with 3-day pyronaridine / artesunate treatment.

Electrocardiogram (ECG) findings of any clinically significant abnormalities were very few and do not suggest a safety concern with pyronaridine /artesunate treatment. No ECG conduction or rhythm changes have been identified in association with pyronaridine / artesunate treatment.

### *5.2.3 Posology*

The food effect study did not suggest any clinically relevant effect of food on the bioavailability of either compound and therefore can be taken with or without food. The tablets and the granules should be stored in their original pack until use.

**PYRAMAX tablets** are immediate release, orange, round, film-coated tablets. Each tablet contains 180 mg of pyronaridine tetraphosphate and 60 mg of artesunate.

The tablet is a non-scored, single dose strength, to be administered once a day, by weight (15 to 90 kg) in ranges of 1 to 4 tablets.

| Weight | No. of Tablets | Pyronaridine (mg/kg) |
|---|---|---|
| 15 - < 24 kg | 1 | 7.5 – 12.0 |
| 24 - < 45 kg | 2 | 8.0 – 15.0 |
| 45 - < 65 kg | 3 | 8.3 – 12.0 |
| 65 - < 90 kg | 4 | 8.0 – 11.1 |

**PYRAMAX granules**

| Weight | No. of Granule Sachets | Pyronaridine (mg/kg) |
|---|---|---|
| 5 - < 8 kg | 1 | 7.6 – 12.0 |

| | | |
|---|---|---|
| 8 - < 15 kg | 2 | 8.1 – 15.0 |
| 15 - < 20 kg | 3 | 9.0 – 12.0 |
| 20 - < 25 kg | 4 | 9.6 – 12.0 |

## 5.3 Stability of the formulations

### PYRAMAX tablets

*PYRAMAX* tablets will be packaged into tropical blister packs. One tropical blister pack contains 9 tablets in a 3 x 3 orientation. One or ten blister packs are inserted into a printed paper carton. The blister packs comprise a thermoformed PVC film with an aluminium lid foil and an aluminium cold-formed laminate.

Based on the available data from the primary batches of drug product, the Sponsor has assigned an 18 month shelf-life to *PYRAMAX* tablets at March 2010 when stored at or below 30°C.

The shelf-life will be extended from 18 to 24 months based on 18 months acceptable real time data.

### PYRAMAX granules

*PYRAMAX* granules will be packaged into stick pack sachets in a pillow bag.
One stick pack sachet contains 60mg pyronaridine tetraphosphate and 20mg artesunate.

The number of sachets required are inserted into a printed paper envelope by the prescribing health worker.

The sachet packs comprise special sealant (Surlene), aluminium foil and PET.

Based on available data from the primary batches of drug product, the Sponsor has assigned an 18month shelf-life to *PYRAMAX* sachets at November 2010 when stored at or below 30°C.
The shelf-life will be extended from 18 to 24 months based on 18 months acceptable real time data.

### Storage conditions

The manufacturer recommends that the drug is stored below 30°C in the original package in order to protect from heat, light and humidity.

# 6. INTERNATIONAL AVAILABILITY – SOURCES, IF POSSIBLE MANUFACTURERS

## 6.1 Sources and manufacturers

Pyronaridine/artesunate fixed dose combination tablets and granules are manufactured by:

Shin Poong Pharmaceutical Co., Ltd
408-4, Moknae-Dong, Ansan-Si,
Kyunggi-Do
Korea

This facility has been constructed and equipped in line with EU Good Manufacturing Practice (GMP) and will have been Inspected by the European Medicines Agency (EMA) January 2011 as part of the review of the Article 58 Submission for Opinion Status. Inspection by WHO prequalification inspection is pending.

Sufficient quantities of tablet and granules are to be manufactured to meet expected needs.

Both pyronaridine tetraphosphate and artesunate are manufactured at the same site as the tablet and granule formulations. Active ingredients are GMP compliant.

## 6.2 History of the product

### *6.2.1 Background on artemisinin-based combinations (ACTs)*

Artemisinin derivatives, including artesunate, are widely used antimalarial drugs, clearing parasites rapidly; however conventional 5-7 day monotherapy regimes are associated with recrudescence (Barradell and Fitton 1995). Furthermore, resistant strains of *P.falciparum* might develop if artemisinin derivatives are used alone. Therefore, to ensure high cure rates with short-course, three day therapy, artemisinin-based combinations like artesunate+amodiaquine or artesunate+mefloquine are recommended (WHO, 2006). Artemisinin derivatives have been administered to more than a million patients with malaria and reports show that it is well tolerated and safe (Davis *et al*, 2005, Van der Meersch 2005). Artesunate tablets and injection have been registered in Brazil, China, Ghana, Burma, Thailand and Vietnam for more than 20 years (White 1994).

Artemether/lumefantrine (Riamet®, Coartem®) is currently the only fixed-dose, artemisinin based combination registered with a competent stringent regulatory Authority and based on internationally recognised guidelines (WHO, 2006). The six dose regimen is highly efficacious against multidrug resistant *P. falciparum* (Vugt *et al*, 1999, Bakshi

*et al*, 2000). Riamet® is available in developed, non-endemic countries and Coartem® is registered and marketed in malaria-endemic countries. A newly paediatric formulation for infants and children under 11 kg has been recently approved and is currently deployed in malaria-endemic countries The partner drug, Lumefantrine, has to be given with food to ensure adequate absorption and thus efficacy which causes problems in treating children with malaria.

### *6.2.2 Rationale for Development*

The goal of anti-malarial drug development is to develop potent, safe, easy-to-administer, and inexpensive combination therapies. There is a need for new drugs that are efficacious against both *P. falciparum* and blood stage of *P. vivax*, because in areas where both species exist and health systems are undersourced, it is often not possible to distinguish between the 2 species at the initial diagnosis. Given the data accumulated to date, it is anticipated that the combination of pyronaridine tetraphosphate and artesunate as a fixed dose ACT, will fulfil these needs.

Artesunate is the most widely used member of the artemisinin derivative drugs. It is effective against strains of *P. falciparum* resistant to all other antimalarial drugs in common clinical practice, as well as *P. vivax*.

Pyronaridine tetraphosphate is a blood schizonticide antimalarial therapy synthesised in China in 1970. Available data indicate that pyronaridine is effective in cases of chloroquine resistance and seems to be satisfactorily tolerated (Zheng *et al*, 1982). Pyronaridine (oral and injectable formulations) is currently marketed in China under the trade name Malaridine and is also being reported as administered in combination with other agents with the aim of preventing the appearance of drug resistance (Ringwald *et al*, 1999, Chen and Zheng, 1992). The physicochemical properties of pyronaridine have been recently determined (Olajire *et al,* 2006).

A fixed-dose combination of pyronaridine /artesunate 3-day treatment, will shorten the course of artesunate therapy, and is predicted to provide high cure rates, decreased recrudescence and delay the development of resistance to artesunate.

Pyronaridine and artesunate are antimalarial agents with a history of clinical use both separately and in combination with other drugs. Each drug has powerful schizonticidal actions but the combination of the two is expected to show pharmacological addition in man. The action of artesunate is a rapid knock-down of the parasites, after which the drug is rapidly cleared as it has a short systemic half-life. Pyronaridine is also effective in the short-term but has an intermediate blood half-life thus providing a sustained schizonticidal effect. The aim of the fixed dose combination of pyronaridine /artesunate in the treatment of uncomplicated acute malaria is to provide a rapid reduction in

parasitaemia with a three-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

Based on existing clinical data and clinical practice, the ratio of pyronaridine to artesunate of 3:1 w/w has been developed. Doses have been selected to be in line with current prescribing practise or reported literature basis for the agents when used as monotherapy.

A full package of regulatory compliant pre-clinical studies on pyronaridine /artesunate alone and in combination, has been conducted to GLP standards. The drug materials have been produced to GMP standard by the Manufacturer, Shin Poong Pharmaceuticals Co Ltd (SPP). The GCP drug development programme for pyronaridine /artesunate has been designed to meet a target product profile for blood stage curative treatment of a once daily administration of a fixed dose tablet or granule paediatric formulation pyronaridine /artesunate, for 3 days to patients with acute uncomplicated malaria.

In this development programme artesunate is being partnered with an established antimalarial agent, pyronaridine. The objective of the programme is to develop a three day fixed dose oral therapy for use in infants, children and adults to treat acute, uncomplicated malaria for both *P. falciparum* and blood stages of *P. vivax* as an alternative to current malaria treatments, especially in areas where resistance to existing therapy against *P. falciparum* is a concern. Pyronaridine /artesunate is presented as a combined tablet or granule formulation in sachet, enabling adults as well as infants to be treated.

## 6.3 International availability and production capacity

In order to address the concerns of access to product, availability of stock and quality, Shin Poong from the outset chose to produce pyronaridine tetraphosphate and artesunate by itself; controlling the sourcing of starting materials through to distribution employing its own processes and network. In this way Shin Poong can assure adequate production and can be sufficiently flexible to market demands.

The development of pyronaridine tetraphosphate and artesunate tablet and granules was conducted to meet the stringent requirements of the EMA as competent regulatory authority. Nonetheless Shin Poong set out to conduct GCP clinical trials in a broad range of malaria endemic countries such that the product could be tested in the widest range of settings. Shin Poong were committed to ensure that both Plasmodium species should be fully tested to provide physicians with greater treatment flexibility in regions where mixed *falciparum* and *vivax infection* is prevalent. Furthermore, the development phase of the tablet and the granules formulation took place in parallel so that the target population of children could be exposed to the drug within the same timeframe as the adult.

Shin Poong elected to follow the newly created Article 58 Opinion Route for product registration as it provided for involvement of WHO both in the review of the registration

dossier as well as facilitating WHO prequalification for artemisinin based antimalarial products.

A submission to Korean Food Drug Agency (K-FDA) took place in August 2010, in parallel to that of EMA. Subsequent registrations will follow through Shin Poong Affiliates in endemic countries.

Shin Poong production capacity is as follows:

| | Annual Capacity in 2011 | Annual Capacity in 2014 |
|---|---|---|
| Tablet | 67 Millions treatment | 110 Millions treatment |
| Granule | 34 Millions treatment | 70 Millions treatment |

# 7. WHETHER LISTING IS REQUESTED AS AN INDIVIDUAL MEDICINE OR AS AN EXAMPLE OF A GROUP

It is proposed that pyronaridine tetraphosphate/artesunate tablet and granules are listed in the WHO Model Lists of Essential Medicines (Adults and Children) in
sub-section 6.5.3: antimalarial medicines – curative treatments in "antimalarial medicines for curative treatment"

While other fixed dose combination ACTs are listed in the Essential Medicines List (artemether/lumefantrine (20mg/120mg) combination tablets; EML March 2009), pyronaridine tetraphosphate/artesunate tablet and granules provide the advantage that it can be prescribed for both *Plasmodium falciparum* and *Plasmodium vivax* malaria. The two formulations also provide the prescriber with greater options when treating younger children, as the target population. The weight based treatment bands for dosing and once a day dosing provide further advantages and should improve treatment compliance.

# 8. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE (EPIDEMIOLOGICAL INFORMATION ON DISEASE BURDEN, ASSESSMENT OF CURRENT USE, TARGET POPULATION)

*P. falciparum* is the most severe form of malaria affecting millions of people every year with its greatest prevalence in sub-Saharan Africa. Malaria is spread by the bite of the *Anopheles* mosquito. The disease mainly affects the under fives from about four months of age and children may have up to six episodes of malaria each year. Partial immunity develops later in childhood though repeated cycles of infection. More than 500,000 African children develop cerebral malaria (a severe form of the disease that affects the brain) each year, and 10-20% of these children die and approximately 7% are left with permanent neurological damage.

*P. falciparum* infection during pregnancy increases the chance of maternal anaemia, abortion, stillbirth, prematurity, intrauterine growth retardation, and low infant birth weight. Maternal anaemia, due to malaria, is estimated to cause as many as 10,000 maternal deaths each year in Africa. Malaria has been estimated to cause 8% to 14% of all low birth weight babies. Low infant birth weight is the greatest single risk factor for death in the first month of life.

Common co-morbidities found within the African population include malnourishment, low haemoglobin levels, HIV infection and tuberculosis (TB).

*Plasmodium vivax* (*P. vivax*) represents a major health problem throughout the tropics. Outside of Africa, it accounts for over 50% of malaria cases, affecting an estimated 70-80 million people per year, notably in Southeast Asia, India and Central and South America, and has a particularly strong impact on the archipelago of Indonesia as well as in Papua New Guinea. In addition, it is estimated that 10-20% of the *P. vivax* cases occur in Eastern and Southern Africa, while *P. vivax* cases are extremely rare in the countries of sub-Saharan West Africa. This is apparently due to the high prevalence of the Duffy negative trait in West Africans, a phenotype that lacks the receptor for invasion of the human red blood cell (RBC) by *P. vivax* merozoites (Mendis K et al. 2001). Furthermore, in recent years the re-emergence of *P. vivax* has become a major problem in malaria-endemic areas, such as Korea or China, where the disease had been eradicated many years ago (Sleigh AC et al. 1998; Chai JY et al. 1999; Oh MD et al. 2001).

The *P. vivax* infection is rarely life-threatening, but is responsible for an important morbidity in all age groups (Karunaweera ND et al. 2003). *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 (Krotoski WA et al. 1982). Thus, a single infection causes repeated bouts of illness that significantly impact subjects' health and ability to carry on activities of daily living. *P. vivax* causes a debilitating febrile illness with fevers as high as 39-41°C. Other major symptoms include headache, myalgia,

nausea, diarrhoea, and vomiting. In the majority of cases, *P. vivax* malaria is benign and vital organ dysfunction is very rare. Nevertheless, reports of cases of severe *P. vivax* malaria have been published and acute respiratory distress syndrome seems to be one of the more common complications (Kochar DK et al. 2005).

| Indication/target population | Uncomplicated malaria caused by *P. falciparum* and *P. vivax* |
|---|---|
| Incidence of target indication Prevalence/Incidence of target indication and potential health risk | An estimated 3.3 billion people were at risk of malaria in 2006. Of this total, 2.1 billion were at low risk (< 1 reported case per 1000 population), 97% of whom were living in regions other than Africa. The 1.2 billion at high risk (≥ 1 case per 1000 population) were living mostly in the WHO African (49%) and South-East Asia regions (37%).<br><br>There were an estimated 243 million episodes of malaria in 2008, with a wide uncertainty interval (5th–95th centiles) from 190 million to 311 million cases. Eighty-six percent, or 208 million (155–276 million) cases, were in the African Region. Eighty six percent of the cases in Africa were in 13 countries, and over half were in Nigeria, Democratic Republic of the Congo, Ethiopia, United Republic of Tanzania and Kenya. Among the cases that occurred outside the Region, 80% were in India, Sudan, Myanmar, Bangladesh, Indonesia, Papua New Guinea and Pakistan (World Malaria Report. WHO 2008 & 2009). |
| Mortality in target indication | There were an estimated 863,000 (708,000–1,003,000) malaria deaths in 2008, of which 88% (767 000, range 621 000 – 902 000 ) were in Africa and 85% were of children under 5 years of age (World Malaria Report. WHO 2009).<br><br>In Africa approximately 88% of cases are in children <5 years of age; in South East Asia the number is closer to 34%. The approximate mean ages in the Phase II and Phase III children-only performed for *PYRAMAX* was 5.5 years and 5 years respectively. |

## *TARGET POPULATION AND RATIONALE ON THE RATIO/DOSE*

### Target Population

*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 granules are indicated for the treatment of acute, uncomplicated

malaria infection caused by *Plasmodium falciparum* in patients weighing 5 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.

**Rationale on ratio/dose**

**The single strength of pyronaridine / artesunate TABLET contains 180 mg pyronaridine tetraphosphate and 60 mg artesunate.**

**The single strength of pyronaridine / artesunate GRANULES contains 60 mg pyronaridine tetraphosphate and 20 mg artesunate.**

It has been shown that pyronaridine is active *in vitro* against *Plasmodia* species, laboratory and field isolates, both sensitive and resistant to other agents such as chloroquine with an $IC_{50}$ of the order of 8 nmol/l. Artesunate, and its active metabolite dihydroartemisinin (DHA), are also active against a similar range of *Plasmodi*a species with $IC_{50}$ values of the order of 4 and 1.5 nmol/l, respectively.

Pyronaridine / artesunate alone inhibited *P. chabaudi* in mice at 12 and 4 mg/kg, respectively for three days. A combination of a 3:1 ratio of the two drugs was equally active at 8 mg/kg (6 + 2 mg/kg).

Ringwald *et al.* (1999) previously reported weak antagonism when a combination of pyronaridine and dihydroartemisinin were examined against chloroquine- sensitive and resistant isolates of *P. falciparum in vitro*. Similarly, mild antagonism has been reported by other investigators using a similar combination against *P. falciparum* (Davis *et al*, 2006; Vivas *et al*, 2008).

In contrast, when 3 strains of *P. falciparum* were incubated for 48 hours with a combination of pyronaridine and artemisinin, the data indicated at least an additive but, predominantly, a synergistic effect of this combination (Gupta *et al*, 2002). The authors suggested that the differences between these findings may be explained by differences in methodology and modes of calculation. Moreover, it should be noted that whilst antagonism has been reported between pyronaridine and artemisinin *in vitro* this is not usually translated *in vivo* (Vivas *et al,* 2008).

The efficacy of combinations of pyronaridine with both artemisinin and artesunate has been studied *in vivo*. In mice infected with chloroquine-sensitive *P. yoelii* ssp. [either NS or one of two lines derived from it namely ART (resistant to artemisinin) or SPN (resistant to pyronaridine)], the blood schizontocidal effects of subcutaneously administered combinations of artemisinin and pyronaridine (using the $ED_{90}$'s for either compound) were evaluated. Combinations of artemisinin and pyronaridine were

additive against *P. yoelii* NS but, showed marked synergy (as assessed using isoboles) against both the ART and SPN lines (Peters and Robinson, 1997).

Additional studies in mice infected with chloroquine-sensitive *P. berghei* (N strain) demonstrated that a combination of artesunate with pyronaridine impeded the selection of resistance to these compounds in *P. berghei* (Peters and Robinson, 2000).

In a recent study (Vivas, personal communication) the efficacy and PK/PD interactions of orally administered pyronaridine in combination with either artesunate or dihydroartemisinin (DHA) in a 3:1 ratio were compared with each drug administered alone in mice infected with *P. berghei* or *P. chabaudi*. In the standard 4-day suppressive test, compared to monotherapy, combinations of pyronaridine /artesunate and pyronaridine /DHA showed comparable efficacy against all parasite strains tested (mean ED90 2.9:0.93 mg/kg and 2.8:0.95 mg/kg) respectively. Indeed, both combinations were more efficacious against the *P. berghei* NY drug sensitive strain, the artesunate resistant *P. berghei* SANA strain, the pyronaridine resistant strain *P. berghei* NPN and the drug-sensitive *P. chabaudi* AS strain when compared to monotherapy.

A fixed-dose combination of pyronaridine / artesunate 3-day treatment, will shorten the course of artesunate therapy, and is predicted to provide high cure rates, decreased recrudescence and delay the development of resistance to artesunate. Because pyronaridine has an intermediate half-life, compared with other antimalarials with substantially longer half lives such as chloroquine and mefloquine, it appears to be an ideal partner drug for artesunate.

Pyronaridine /artesunate are antimalarial agents with a history of clinical use both separately and in combination with other drugs. Each drug has powerful schizonticidal actions but the combination of the two is expected to show pharmacological addition in man. The action of artesunate is a rapid knock-down of the parasites, after which the drug is rapidly cleared as it has a short systemic half-life. Pyronaridine is also effective in the short-term but has an intermediate blood half-life thus providing a sustained schizonticidal effect. The aim of the fixed dose combination of pyronaridine : artesunate in the treatment of uncomplicated acute malaria is to provide a rapid reduction in parasitaemia with a three-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

Based on existing clinical data and clinical practice, **the ratio of pyronaridine to artesunate of 3:1 w/w was developed**. Doses were selected to be in line with current prescribing practise for artesunate and literature-based for pyronaridine when used as monotherapy.

# 9. TREATMENT DETAILS

## 9.1 Method of administration

The dose should be taken orally once a day for three days.

Pyronaridine /artesunate tablets and granules 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.

## 9.2 Dosage

***TABLETS***
*Dosage in adults and children*
Pyronaridine /artesunate tablets should be taken orally as a single daily dose for three consecutive days.

| Body weight | Number of tablets | 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 |

***GRANULES***
*Dosage in children and infants*
Pyronaridine /artesunate granules should be taken orally as a single daily dose for three consecutive days.

| Body weight | Number of granule sachets | Regimen |
|---|---|---|
| 5 - < 8kg | 1 sachet | Daily for 3 days |
| 8 - < 15kg | 2 sachets | Daily for 3 days |
| 15 - < 20 kg | 3 sachets | Daily for 3 days |
| 20 - < 25 kg | 4 sachets | Daily for 3 days |

*Dosage in the elderly*
There is no experience in patients greater than 65 years old
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.

## 9.3 Duration

Pyronaridine /artesunate daily dose is to be administered on 3 consecutive days.

# 10. SUMMARY OF COMPARATIVE EFFECTIVENESS IN A VARIETY OF CLINICAL SETTINGS

Pyronaridine /artesunate clinical efficacy and safety was examined in four controlled and randomised pivotal studies; two controlled phase II studies for dose identification and two controlled studies in healthy volunteers.

The pyronaridine /artesunate clinical study programme consists of the following studies:

**Two Phase I studies in healthy volunteers:**

- Study SP-C-001-03 – A Phase I clinical study to assess the safety, tolerability, pharmacokinetics as well as for potential interaction of orally administered pyronaridine : artesunate in Healthy Korean Subjects.
- Study SP-C-009-08 - Bioequivalence of pyronaridine / artesunate to-be-marketed tablet to the clinical trial reference tablet in Healthy European Subjects.

**Two dose-finding Phase II pyronaridine /artesunate studies in patients with acute uncomplicated *Plasmodium falciparum* malaria:**

- Study SP-C-002-05 - A randomised, multi-centre, Phase II, dose-ranging clinical study to assess the safety and efficacy of fixed-Dose, orally administered pyronaridine /artesunate (3:1) in Adult Subjects from Thailand, Indonesia, Cambodia, Gambia, Senegal and Uganda with acute uncomplicated *Plasmodium falciparum* malaria
- Study SP-C-003-05 - An open-label, Phase II, dose escalation clinical study to assess the pharmacokinetics, safety, tolerability and pharmacodynamics of fixed dose combination tablet of pyronaridine /artesunate (3:1) in children from Gabon with acute uncomplicated *Plasmodium falciparum* malaria and to assess the relative bioavailability of a fixed dose granule formulation of pyronaridine : artesunate (60 mg : 20 mg) for paediatric use, compared with tablets of the same dose in children with acute uncomplicated *Plasmodium falciparum* malaria.

**Four Phase III comparative study of pyronaridine / artesunate:**

- Study SP-C-004-06 – An open label, Phase III Comparative, Randomised, Multi-Centre Clinical Study in South East Asia and in Africa to Assess the Safety and Efficacy of fixed dose formulation oral pyronaridine : artesunate versus mefloquine + artesunate in children and adult patients with acute uncomplicated *Plasmodium falciparum* malaria.

- 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 from Africa, Indonesia and the Philippines with acute uncomplicated *Plasmodium falciparum* malaria.
- 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 from India and South East Asia with acute *Plasmodium vivax* malaria.
- 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 from Africa and the Philippines with acute uncomplicated *Plasmodium falciparum* malaria

A description of the Phase II and Phase III pyronaridine /artesunate clinical development programme is provided:

Phase II Adult Study of pyronaridine /artesunate

In the phase II programme, the strategic focus for the development plan was three-fold. Firstly, this was to enable the dose-finding study which showed that pyronaridine / artesunate cleared parasites from uncomplicated malaria patients within a range of 24 to 28 hours and that the fixed dose combination was both safe and well tolerated at all doses studied. Secondly, it was to justify the tablet strength (180:60) and the dose level of pyronaridine /artesunate fixed combination for use in phase III study and marketing. Thirdly, it was to test pyronaridine /artesunate as a fixed-dose combination in the age range of patients which are the most affected by malaria and to conduct such trials in endemic regions, including those in areas of known current antimalarial resistance.

The phase II double blind dose ranging study has been conducted comparing safety and efficacy of one of three doses of the fixed pyronaridine /artesunate combination (6:2mg/kg, 9;3mg/kg, 12:4mg/kg) as a once daily oral dose for the treatment of uncomplicated acute *Plasmodium falciparum* malaria. The trial was conducted in 6 countries in South East Asia and Africa. The study commenced mid July 2005 and was

completed in mid April 2006. Primary outcome measure was PCR-corrected adequate clinical and parasitological response (ACPR) at Day 28. Other outcome efficacy and safety assessments included ACPR on Day 42, parasite clearance time (PCT), fever clearance time (FCT) as well as ECG, clinical laboratory findings and adverse events, plus pharmacokinetics in a sub-group. Four Hundred and Seventy Seven (477) patients were treated in the trial at doses of 6:2, 9:3 or 12:4 mg/kg (160:157:160 patients respectively).

**Efficacy analysis**

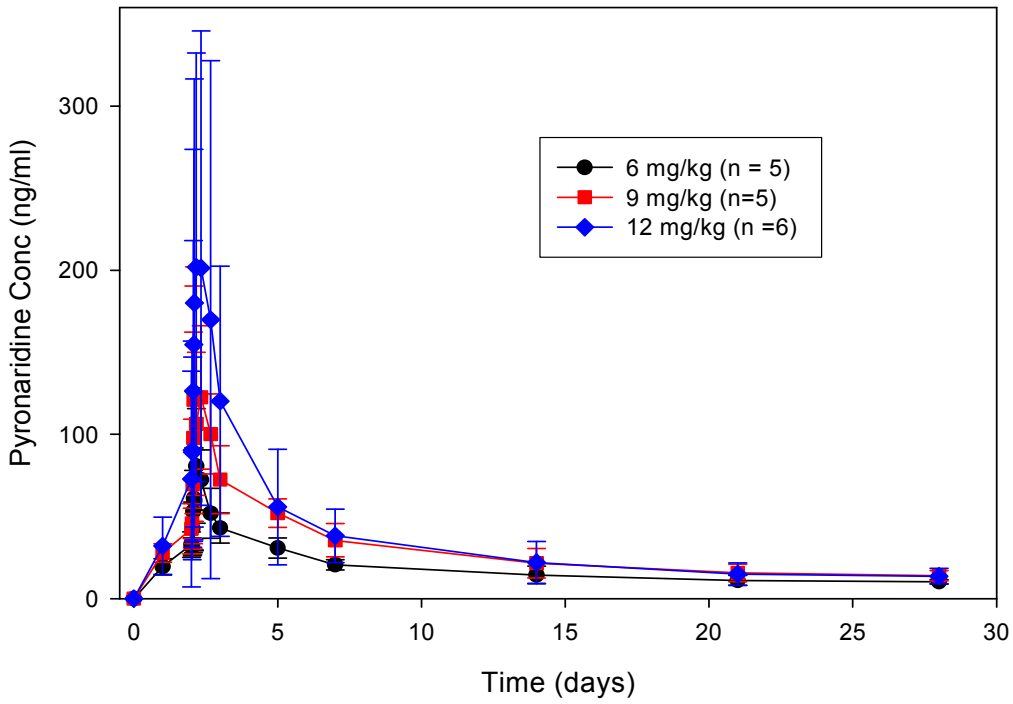
In the per protocol analysis (EE population), at doses of 6:2, 9:3 or 12:4 mg/kg of pyronaridine /artesunate, PCR corrected ACPR was 100 % at Day 14, 96.5%, 99.3%, 99.3% respectively at Day 28 and 94.9%, 97.9%, 97.9% respectively at Day 42. Parasites were cleared by 30 hours in each dose group. Fever clearance time was a mean of 25.8 hours across all dose groups. Any treatment failures were late clinical or late parasitological failures. There were no early treatment failures. There were no overall regional differences in the efficacy of pyronaridine /artesunate.

**Pharmacokinetic analysis**

With regard to the pharmacokinetics of pyronaridine in this Phase II study of pyronaridine / artesunate, it was seen that the $T_{max}$ after the third dose was approximately 6 hours after oral administration. The mean $C_{max}$ values after the third dose were 91.9, 156.8 and 226.1 ng/ml at the 6, 9 and 12 mg/kg dose level, respectively. The pyronaridine half-life was approximately 10.4 to 15.1 days. This elimination half-life is similar to that found in a bioequivalence study where the average elimination half-life was 14.1-14.2 days. This elimination half-life is longer compared to healthy adult subjects (6.6 to 9.7 days) and children with malaria (6.6 to 9.0 days), which may be a reflection of the longer blood sampling period used in this study. Compared with phase I results, AUC values were slightly lower in malaria patients, which may reflect a larger pyronaridine volume of distribution in malaria patients.

Considering the efficacy and the safety findings, both the 9+3 mg/kg dose and the 12+4 mg/kg dose are clinically useful and safe in the treatment of *P. falciparum* malaria. The 6+2 mg/kg dose is also effective and safe but was not demonstrated to result in a PCR-corrected ACPR statistically significantly greater than 95%.

**Figure 1. Mean (± SD) Pyronaridine Blood Levels over 25 days**




***Phase II Paediatric Study of pyronaridine /artesunate***

A dose rising paediatric study in uncomplicated *Plasmodium falciparum* malaria was conducted at Albert Schweitzer Hospital in Lambaréné, Gabon, from June to December 2006 in children over 2 years old and between 10 and 40 kg. A total of 59 patients (60 planned) received one of the three doses of the pyronaridine /artesunate tablet combination (6:2 mg/kg, 9:3 mg/kg, 12:4 mg/kg) or a 9:3 mg/kg granule formulation as a once daily oral dose for the treatment of uncomplicated disease in a hospital in-patient setting. Fifteen patients per dose were studied with a safety review prior to dose escalation. Treatment was administered once daily for three days and patients were followed up weekly for a 6 week period with a primary endpoint of 28 day PCR-corrected ACPR.

The objective of the trial was to determine pharmacokinetics as well as safety and tolerability of the three doses and two formulations. Efficacy was evaluated to include the proportion of patients with PCR-corrected ACPR on Day 28, parasite clearance time, fever clearance time, proportion of treatment success/failures and central ECG review.

## Efficacy analysis

The overall PCR corrected day 28 cure rate was 100% in per protocol analysis at all dose levels. There were no treatment failures in the per protocol population up to Day 28. Three subjects, all from the 9+3 mg/kg tablet group, had re-appearance of parasitaemia, all detected on Day 28. All of these re-appearances were confirmed as new infections by PCR and classed as treatment success.

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. An additional 10 subjects (18.9% of the per protocol population) had re-appearance of parasitaemia during the course of the study after Day 28: 2 (3.8%) on Day 35 (1 from the 9+3 mg/kg tablet group and 1 from the 9+3 mg/kg granule group) and 8 (15.1%) on Day 42 (3 from the 6+2 mg/kg tablet group, 2 from the 9+3 mg/kg tablet group, 2 from the 12+4 mg/kg tablet group, and 1 from the 9+3 mg/kg granule group). Only 2 of these re appearances were confirmed by PCR as recrudescence (on Days 35 and 36). Furthermore, there was 1 subject from the 6+2 mg/kg group who had a PCR-confirmed new infection on Day 21. This subject was not included in the per protocol population due to the anti-malaria treatment administered for this new infection.

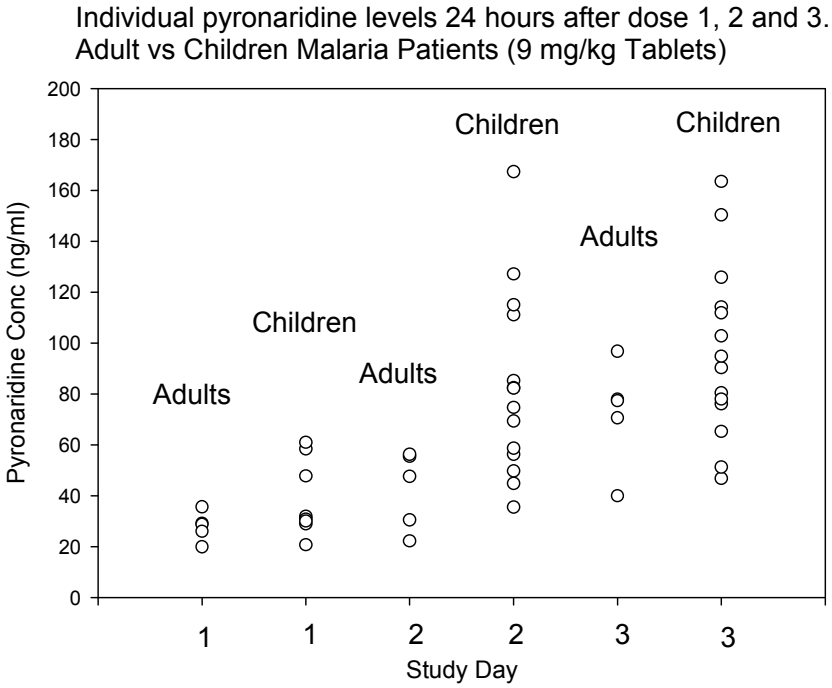
In all treatment groups, rapid parasite clearance was achieved. Median parasite clearance time (PCT) was 16.4 hours at 6:2 mg/kg, 16.1 hours at 9:3 mg/kg, 8.1 hours at 12:4 mg/kg for tablets and 8.3 hours for the 9:3 mg/kg paediatric granule formulation (per-protocol population). `

Time to fever clearance was only summarised for subjects who had fever at baseline or within the first 24 hours after the start of study treatment. Since only 12 subjects in total had fever during this time, the time to fever clearance estimates are not very meaningful. Median FCT was between 8.2 hours and 8.6 hours in all treatment groups.

## Pharmacokinetic analysis

A comparison of the individual pyronaridine levels 24 hours after doses 1, 2 and 3 for for adults and children is shown in Figure 2 for the 9 mg/kg dose level. While there is considerable variability, on the average children, have slightly higher blood pyronaridine concentrations.

**Figure 2. Pyronaridine Levels in Adults vs. children (9 mg/kg)**




Pharmacokinetic analyses were performed in the two formulations (tablets and granules) and results were comparable (Figure 3 and Figure 4).

**Figure 3. Summary of Artesunate Plasma Levels in Tablet vs. Granules**

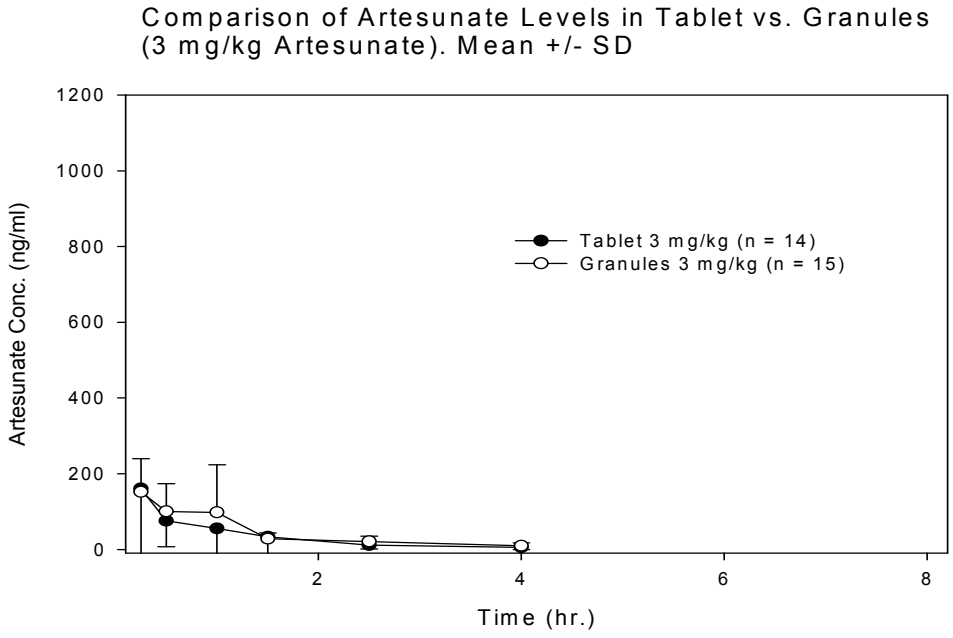
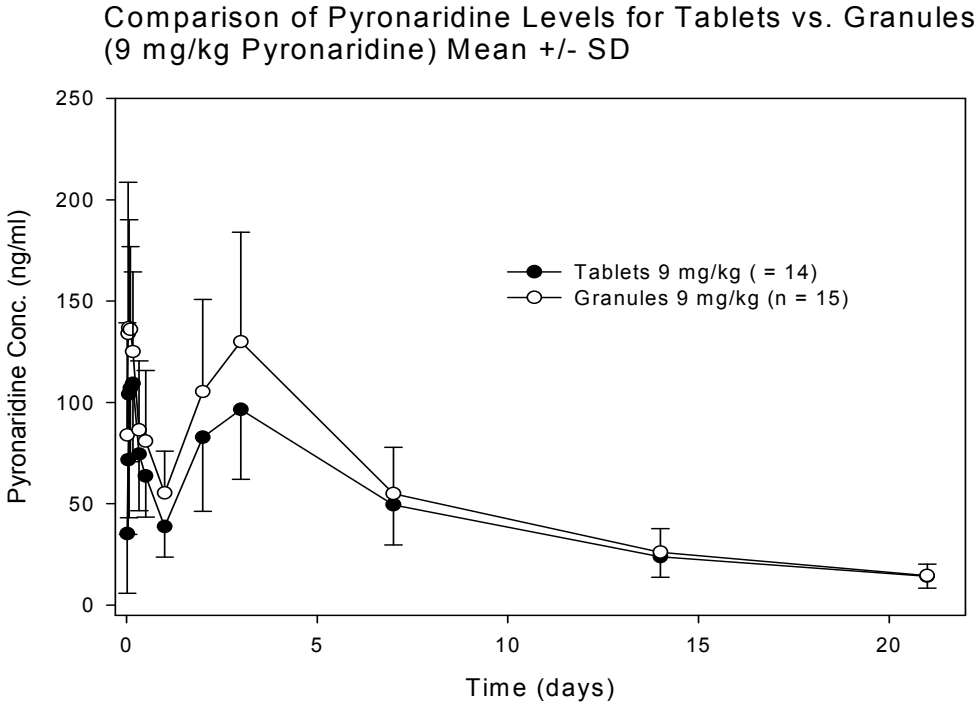


**Figure 4. Summary of Pyronaridine Levels in Tablet vs. Granules**




For artesunate and its active metabolite DHA, a dose-related linear increase in $C_{max}$ and AUC was observed after oral administration of the 6+2 mg/kg, 9+3 mg/kg, and 12+4 mg/kg tablets. The mean Tmax for artesunate and DHA ranged from 0.5 to 1.03 hours and 1.31 to 1.7 hours, respectively. The mean half-life for artesunate and DHA ranged from 0.54 to 1.18 hours and 0.91 to 1.18 hours, respectively. No significant difference in the bioavailability of artesunate or DHA following was observed after oral administration of either the 9+3 mg/kg tablet or granule formulations.

A dose-related linear increase in $C_{max}$ and AUC was observed for pyronaridine after oral administration of the 6+2 mg/kg, 9+3 mg/kg and 12+4 mg/kg tablets. The mean $T_{max}$ for pyronaridine ranged from 2.4 to 3.2 hours and the mean half-life ranged from 6.6 to 9.0 days. There was no significant difference in pyronaridine AUC between the tablet and granule formulations; however, Cmax after the first dose was significantly higher for the granule formulation.

The pyronaridine PK data for the Phase II are similar to those of the healthy volunteer Phase I study (Table 1 ).

**Table -1 Pyronaridine PK parameters Phase II**

| Dose | $T_{max}$ | $C_{max}$ | AUC | $T_{½}$ |
|---|---|---|---|---|
| **(mg/kg)** | **(h)** | **(ng/ml)** | **(ng/ml*d)** | **(d)** |
| **6** | 5.3 | 91.9 | 749 | 19.1 |
| | ±2.0 | ±30.8 | ±603 | ±5.9 |
| **9** | 6.2 | 156.8 | 1036 | 15.9 |
| | ±6.3 | ±57.1 | ±286 | ±5.0 |
| **12** | 7.6 | 226.1 | 1134 | 14.6 |
| | ±4.9 | ±157.5 | ±624 | ±6.6 |

### *Overall conclusion from phase II studies*

The outcome of the phase II dose ranging trials provided sufficient confidence to move into expanded phase III confirmatory trials. Although the sample size within each dose group was small in the paediatric trial, 28-day PCR corrected ACPR as well as parasite clearance time showed promising efficacy of a fixed dose combination of pyronaridine / artesunate in younger patients. All doses of pyronaridine /artesunate were well tolerated. Although no major differences between the doses employed in the study were apparent there appeared to be more cases of malaria reported as AEs in the lowest dose and the adverse event/laboratory parameter profile was marginally worse in the highest dose group. Therefore the dose ratio of 9:3 mg/kg of pyronaridine /artesunate was selected for phase III.

### *Phase III studies with pyronaridine /artesunate*

Phase III comparative study of pyronaridine /artesunate with mefloquine+artesunate in children and adults (*P.falciparum*)

The main objectives of this open label Phase III comparative, randomised, multi-centre, clinical study in South East Asia and Africa, were to compare the efficacy and safety of the fixed combination of pyronaridine /artesunate tablets with that of mefloquine and artesunate (MQ + AS) in subjects with acute, uncomplicated *P. falciparum* malaria and to confirm that pyronaridine /artesunate was non-inferior to MQ + AS in terms of efficacy.

The study was conducted in a total of 1271 male and female, children and adults subjects, recruited from 9 sites in Thailand, Vietnam, Cambodia, India, Ivory Coast, Burkina-Faso and Tanzania, and took place from late January 2007 to early October 2008. The majority of subjects were from Asia (81.3%).

Subjects were randomised in a 2:1 ratio (848 in the pyronaridine /artesunate group and 423 in the MQ + AS group) to receive either oral pyronaridine /artesunate (180:60-mg tablets) once a day for 3 consecutive days (Days 0, 1, and 2) or mefloquine (MQ) (250-mg tablets) plus artesunate (AS) (100 mg tablets) once a day for 3 consecutive days (Days 0, 1, and 2). For pyronaridine /artesunate, the actual dose range covered by this regimen was 7.2:2.4 mg to 13.8:4.6 mg. Posology was based on body weight ranges for both pyronaridine /artesunate and MQ + AS regimens.

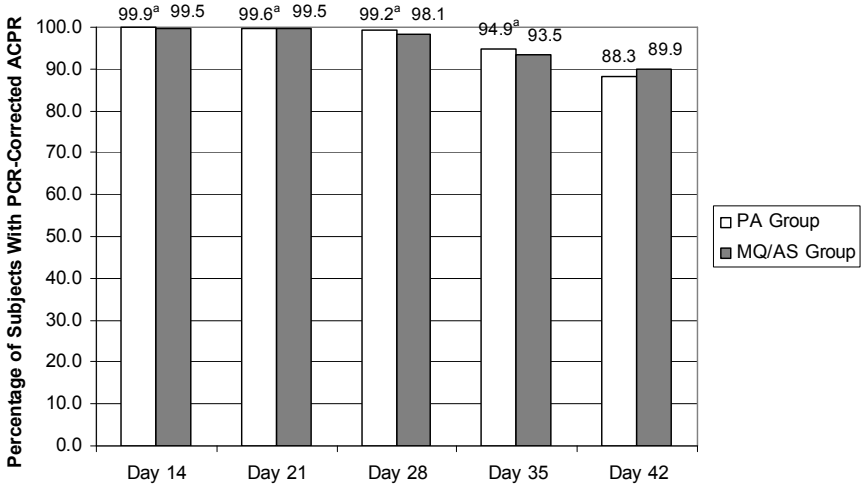
Subjects were followed for 42 days, with the primary efficacy end point of PCR-corrected ACPR occurring 28 days after initiation of study drug administration. Subjects were confined to the study facility for ≥4 days (Days 0, 1, 2 and 3) and ideally remained in the vicinity of the study site for ≥7 days or until fever and parasite had been cleared for ≥24 hours, whichever occurred later. The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

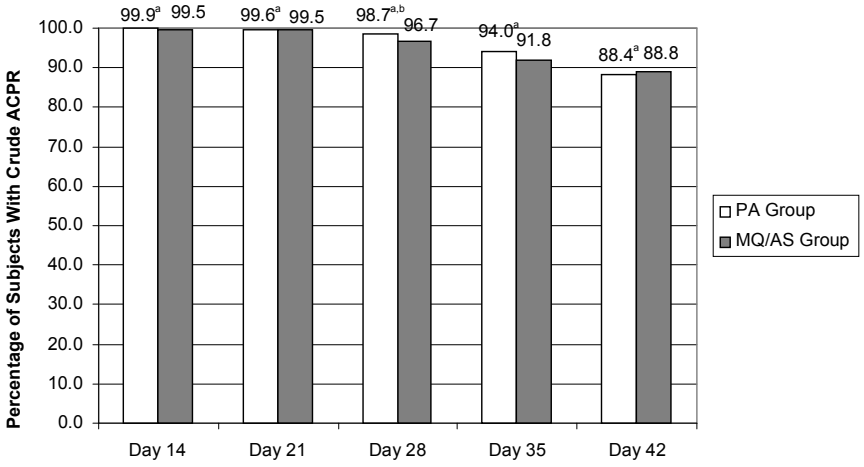
Most subjects were male (75.8%) and Asian/Oriental (81.3%); mean age was 25.1 years. The majority of subjects completed treatment (99.1%) and completed the study (85.0%). The most common reasons for withdrawing from the study were *P. falciparum* parasite re-appearance.

**Efficacy analysis**

For the primary end point, non-inferiority of pyronaridine /artesunate (PA) compared with MQ + AS was demonstrated for PCR-corrected ACPR on Day 28 in the EE population (99.2% PA, 98.1% MQ + AS). In the same population, non-inferiority of PA to MQ + AS was also concluded at Days 14, 21, and 35 for PCR-corrected ACPR (Figure 5), but not at day 42 (88.3% in the PA group and 89.9% in the MQ + AS group. For crude ACPR, PA was non-inferior to MQ + AS at all time points, with the cure rate in the PA group statistically significantly superior to that in the MQ + AS group on Day 28 (98.7% vs. 96.7%). In the ITT population (Figure 6), PCR-corrected and crude cure results were similar, and non inferiority was also demonstrated at day 42 in both PCR-corrected and crude ACPR. No clinically important subgroup (region, age, gender, actual study drug dosing, and previous episode of malaria) differences in Day 28 PCR-corrected ACPR were observed.

**Figure 5. Days 14, 21, 28, 35, and 42 ACPR – EE Population**



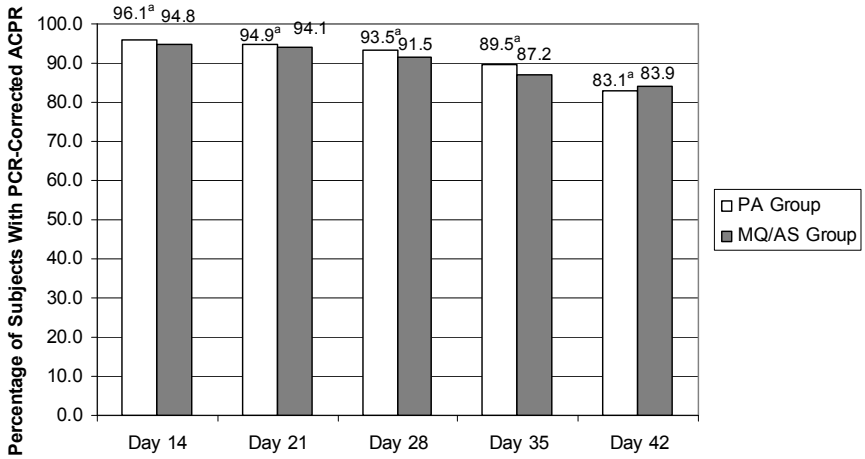



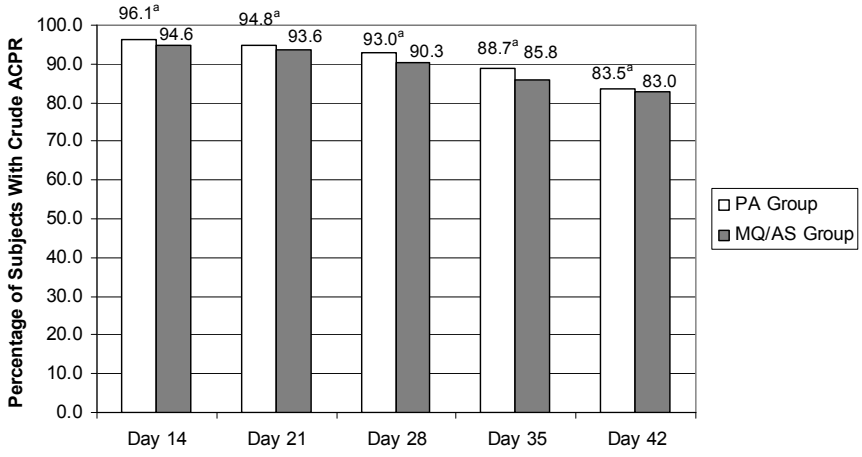

Note: The Day 21 and Day 35 analyses were performed post hoc.

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%.

b. Superiority of PA over MQ + AS was concluded.

**Figure 6. Days 14, 21, 28, 35, and 42 ACPR – ITT Population**



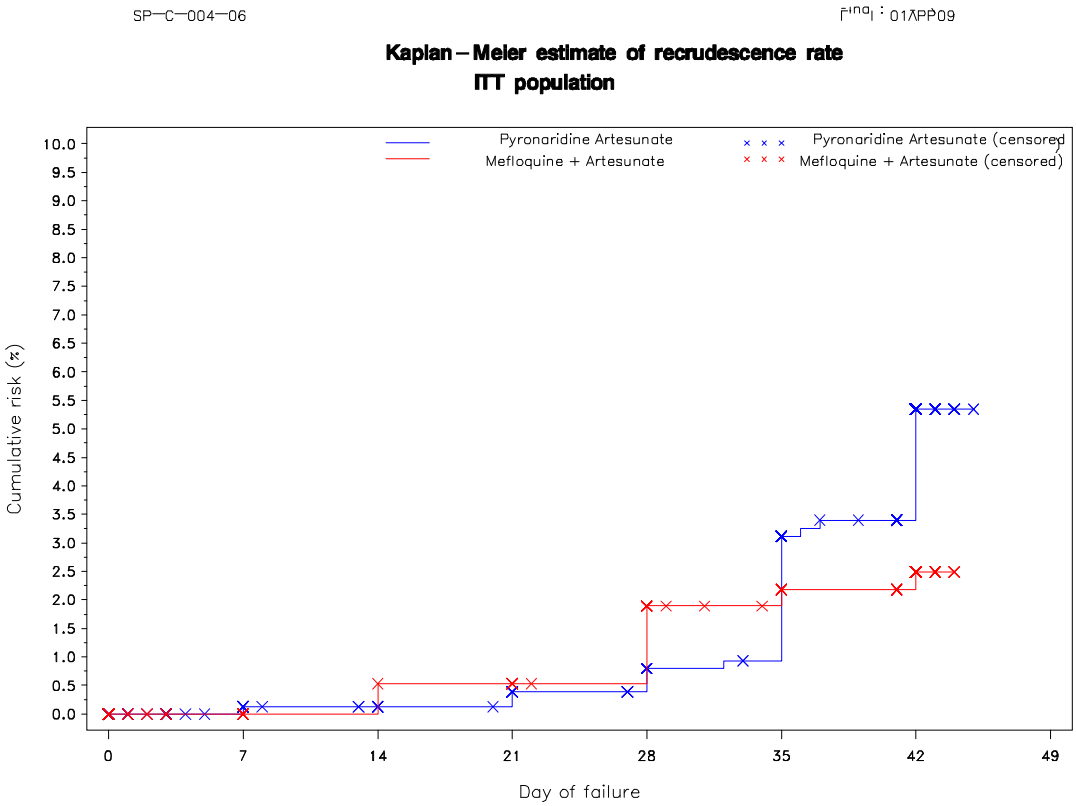




Note: The Day 21 and Day 35 analyses were performed post hoc.

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%.

The parasitology re-appearance (new infection or recrudescence) rate and the recrudescence rate (Figure 7) were statistically significantly lower with pyronaridine / artesunate compared with MQ + AS based on Kaplan-Meier estimates through Day 42 ($p \leq 0.049$). The rate of new infection was statistically significantly lower ($p=0.041$) with pyronaridine /artesunate compared with MQ + AS through Day 28, but not through Day 42.

**Figure 7. Kaplan-Meier Estimates of Recrudescence Rate – ITT Population**




Pyronaridine /artesunate and MQ + AS groups were rapidly effective. Parasite count (*P. falciparum* asexual forms) decreased rapidly (during the first 16 hours) in both the pyronaridine /artesunate and MQ + AS groups; time to parasite clearance was not statistically significantly different between the 2 groups. However, a greater percentage of pyronaridine /artesunate subjects vs. MQ + AS subjects achieved parasite clearance 24 hours after the first dose (38.5% vs. 31.6%). One difference from the main results was that the PCT was prolonged in Pailin (Cambodia) with a median of 64.0h for pyronaridine /artesunate and 64.2h for MQ + AS compared to 31.1h and 31.8h respectively in the other centres. The percentage of patients able to clear their parasites 72h following treatment initiation in Pailin was only 62.9% (95% CI: 54.9-70.8) with pyronaridine /artesunate and 62.0% (95% CI: 50.9-73.1) with MQ + AS. This would appear to represent some evidence of altering sensitivity to artesunate.

Time to fever clearance was similar in the pyronaridine /artesunate and MQ + AS groups.

Phase III comparative study of pyronaridine /artesunate with artemether lumefantrine (Coartem) in children and adults (*P.falciparum*)

This study was a multi-centre, comparative, randomised, (double-blind, double-dummy), parallel-group, non-inferiority study which main objectives were to compare the efficacy and safety of the fixed combination of pyronaridine / artesunate with that of Coartem® (ie, the combination of artemether + lumefantrine [AL]) in subjects with acute, uncomplicated *P. falciparum* malaria and to confirm that pyronaridine /artesunate was non-inferior to AL in terms of efficacy

The study was conducted in a total of 1269 male and female subjects including children (≥20 kg body weight) and adults suffering from acute symptomatic uncomplicated *P. falciparum* malaria recruited from 10 study sites located in Africa and South East Asia (Democratic Republic of Congo, The Gambia, Ghana, Indonesia, Kenya, Mali, Mozambique, The Philippines, and Senegal) from January 2007 to April 2008.

Subjects were randomised to receive either oral pyronaridine /artesunate (180:60-mg tablets) once a day plus AL-placebo (twice a day) for 3 consecutive days (Days 0, 1, and 2) or AL twice a day plus pyronaridine /artesunate -placebo (once a day) for 3 consecutive days (Days 0, 1, and 2) in a 2:1 ratio. The actual dose range of pyronaridine /artesunate covered by this regimen was 7.2:2.4 mg/kg to 13.8:4.6 mg/kg, respectively, which has been shown to be effective and safe in Phase I and II studies. Posology was based on body weight ranges for both the pyronaridine /artesunate and AL regimens.

Subjects were followed for 42 days, with the primary efficacy end point occurring 28 days after initiation of study drug administration. Subjects were confined to the study facility for ≥4 days (Days 0, 1, 2, and 3) and ideally remained in the vicinity of the study site for ≥7 days or when fever and parasite had been cleared for ≥24 hours, whichever occurred later. The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

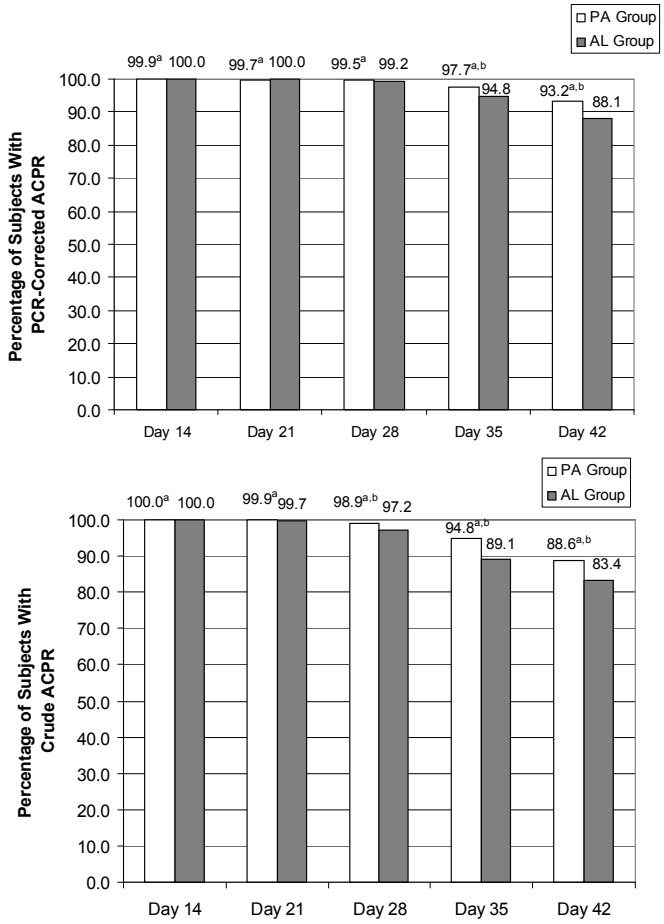
A total of 849 and 423 subjects were randomised to the pyronaridine /artesunate and AL treatment groups, respectively. The majority of subjects were from Africa (84.9%). Most subjects were male (56.7%) and black (84.9%); mean age was 17.5 years. The majority of subjects completed treatment (97.3%) and completed the study (86.3%). The most common reasons for withdrawing from the study were *P. falciparum* parasite re-appearance.

**Efficacy analysis**

Pyronaridine /artesunate was shown to be at least as effective as AL for the treatment of patients with acute, uncomplicated *P. falciparum* malaria. Non-inferiority of pyronaridine / artesunate to AL was demonstrated for PCR-corrected ACPR on Day 28 in the EE (and ITT) population (Figures 8 and 9). Non-inferiority of pyronaridine / artesunate to AL was also demonstrated at all other time points from Day 21 to Day 42 in

the EE population and was maintained in the ITT population. PCR-corrected ACPR was >99% for both treatment groups on Days 14, 21, and 28, and was statistically significantly superior in the pyronaridine /artesunate group compared with the AL group on Day 35 (97.7% vs. 94.8%) and Day 42 (93.2% vs. 88.1%) in the EE population (similar results were observed in the ITT population). A similar pattern of results was observed for crude ACPR (EE and ITT populations).

**Figure 8. - Days 14, 21, 28, 35, and 42 ACPR – EE Population**

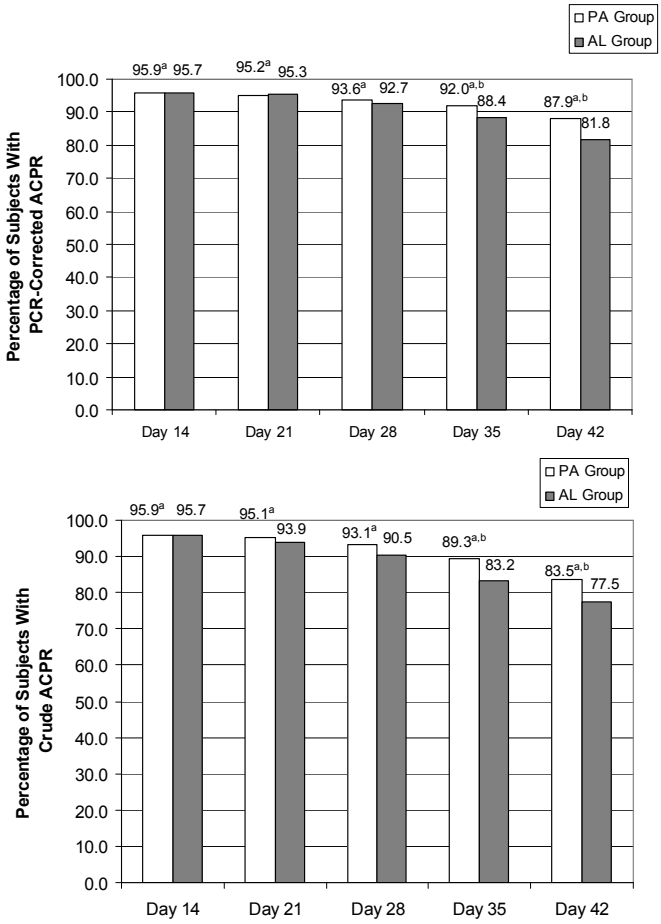



Note: The Day 21 and Day 35 analyses were performed post hoc.

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

**Figure 9. - Days 14, 21, 28, 35, and 42 ACPR – ITT Population**




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%.

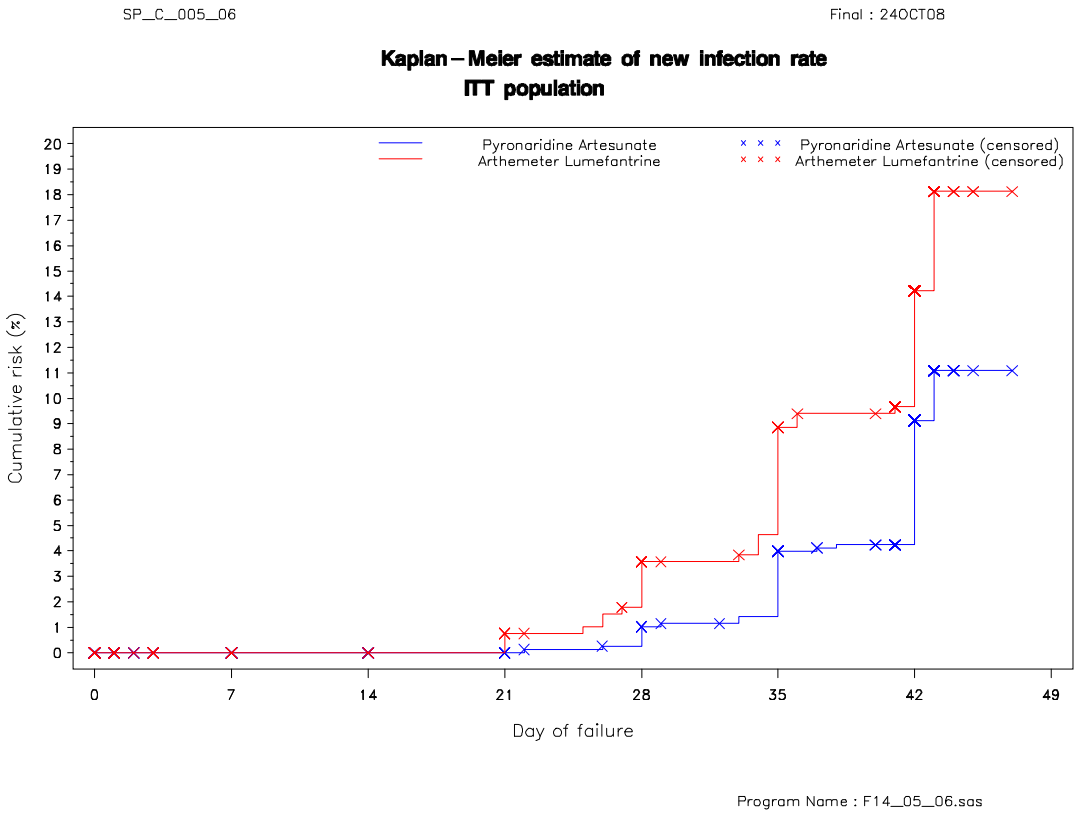
b Superiority of PA over AL was concluded.

No clinically important subgroup (region, age, gender, actual study drug dosing, and previous episode of malaria) differences in Day 28 PCR-corrected ACPR were observed.

There was no statistically significant difference between the pyronaridine /artesunate and AL groups in the Kaplan-Meier estimate of recrudescence rate through Day 28 or Day 42. However, rates of new infection and parasitology re-appearance (new infection or recrudescence) were statistically significantly lower with pyronaridine /artesunate compared with AL ($p<0.008$) through Day 28 and Day 42. The superiority of pyronaridine /artesunate compared with AL for cure rate on Day 42 was likely due to the longer half-life of pyronaridine (17.0 $\pm$ 5.9 days in adults and 16.7 $\pm$ 9.5 days in children under 14 years old, per a phase II – phase III population pharmacokinetics analysis, unpublished data) compared with artemether (3-7 hours), its metabolite dihydroartemisinin (40-60 minutes), or lumefantrine (4-6 days) (Davis *et al,* 2005). The comparatively longer half-life of pyronaridine also likely resulted in the statistically

significantly decreased risk of new infection and parasitology re-appearance compared with AL treatment (Figure 10).

**Figure 10. - Kaplan-Meier Estimates of New Infection Rate – ITT Population**




Pyronaridine /artesunate and AL were rapidly effective. Parasite count (*P. falciparum* asexual forms) decreased rapidly (during the first 16 hours) in both the pyronaridine / artesunate and AL groups. This was not unexpected as the clinical efficacy of the artemisinin derivatives is characterised by an almost immediate onset and rapid reduction of parasitaemia (deVries *et al*, 1996). Time to parasite clearance was statistically significantly ($p<0.001$) shorter in the pyronaridine /artesunate group compared with the AL group. A greater percentage of pyronaridine /artesunate subjects vs. AL subjects achieved parasite clearance 24 hours after the first dose (68.1% vs. 52.8%). Time to fever clearance was similar in the pyronaridine /artesunate and AL groups.

<u>Phase III comparative study of pyronaridine /artesunate with chloroquine in adults (*P.vivax*)</u>

The main objectives of this multi-centre, randomised, double-blind, double-dummy, parallel group comparative trial were to compare the efficacy and safety of the fixed combination of pyronaridine /artesunate (180:60 mg) with that of chloroquine tablets (155 mg), in subjects with acute, uncomplicated *P. vivax* malaria and to confirm that pyronaridine /artesunate was non-inferior to chloroquine in terms of efficacy.

This study was conducted in a total of 456 male and female children (≥20 kg body weight) and adult subjects suffering from acute symptomatic uncomplicated *P. vivax* malaria recruited from study sites located in Cambodia, Thailand, Indonesia and India, from mid March 2007 to end of March 2008. The study was randomised, with a maximum of 160 subjects to be included per site. Subjects were randomised in a 1:1 ratio to receive either oral pyronaridine /artesunate (180:60-mg tablets) plus chloroquine-placebo or oral chloroquine (155 mg tablets) plus pyronaridine / artesunate-placebo, once a day for 3 consecutive days (Days 0, 1, and 2).

For subjects who completed the study up to Day 28 and who had normal glucose-6-phosphate dehydrogenase (G-6-PD) activity, a 14-day course of primaquine (15 mg/day) was administered starting on Day 28, after all required assessments had been performed, to complete their radical cure. Subjects who were deficient in G-6-PD and who completed the study up to Day 28 were treated per country policy.

For pyronaridine /artesunate, subjects received 1 to 4 tablets depending on their body weight. The actual dose range covered by this regimen was 7.2:2.4 mg/kg to 13.8:4.6 mg/kg, which has been shown to be effective and safe in Phase I and II studies. The chloroquine daily dose was 10 mg/kg on Days 0 and 1 and 5 mg/kg on Day 2 for children and 620 mg on Days 0 and 1 and 310 mg on Day 2 for adults.

Subjects were followed for 42 days, with the primary efficacy end point occurring 14 days after initiation of study drug administration. Subjects were confined to the study facility for ≥4 days (Days 0, 1, 2, and 3) and ideally remained in the vicinity of the study site for ≥7 days or when fever and parasite had been cleared for ≥24 hours, whichever occurred later. The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

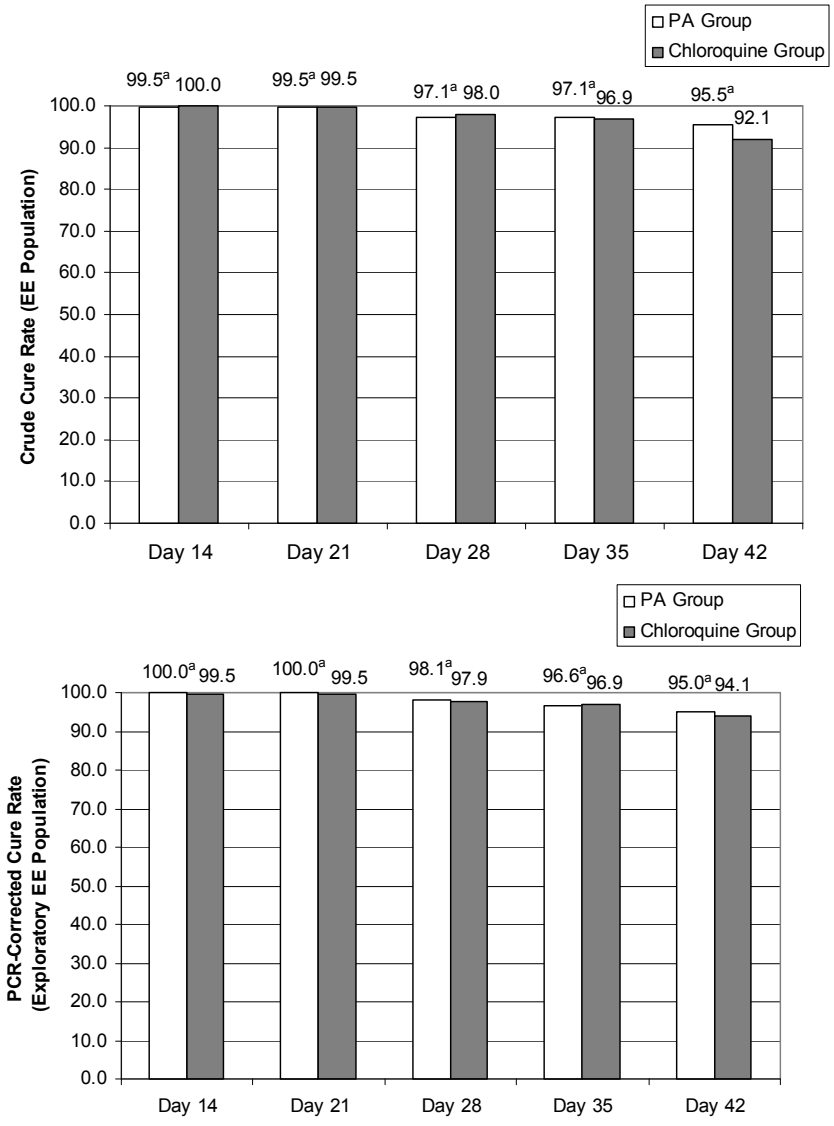
Overall, 33.8% of subjects participated at a site in Cambodia, 17.5% at a site in India, 5.3% at a site in Indonesia, and 43.4% at two sites in Thailand. Most subjects were male (73.7%); mean age was 26.7 years. The majority of subjects completed treatment (97.8%) and completed the study (83.3%). A greater percentage of chloroquine subjects than pyronaridine /artesunate subjects prematurely discontinued, primarily due to infection with *P. falciparum* (6.1% vs. 2.2%).

**Efficacy analysis**

For the primary end point, non-inferiority of pyronaridine /artesunate compared with chloroquine at Day 14 in the EE population was demonstrated for crude cure (99.5% pyronaridine /artesunate, 100.0% chloroquine). Results were similar on Days 21, 28, and 35 and all this results were maintained in the ITT population (Figures 11 and 12). The greatest difference between the pyronaridine /artesunate and chloroquine groups was observed for crude cure rate on Day 42 (95.5% and 92.1%, respectively). The non-inferiority of pyronaridine /artesunate compared with chloroquine was also demonstrated for the exploratory PCR-corrected cure rate (100.0% PA, 99.5% chloroquine) on Day 14. No clinically important subgroup (county, age, gender, by

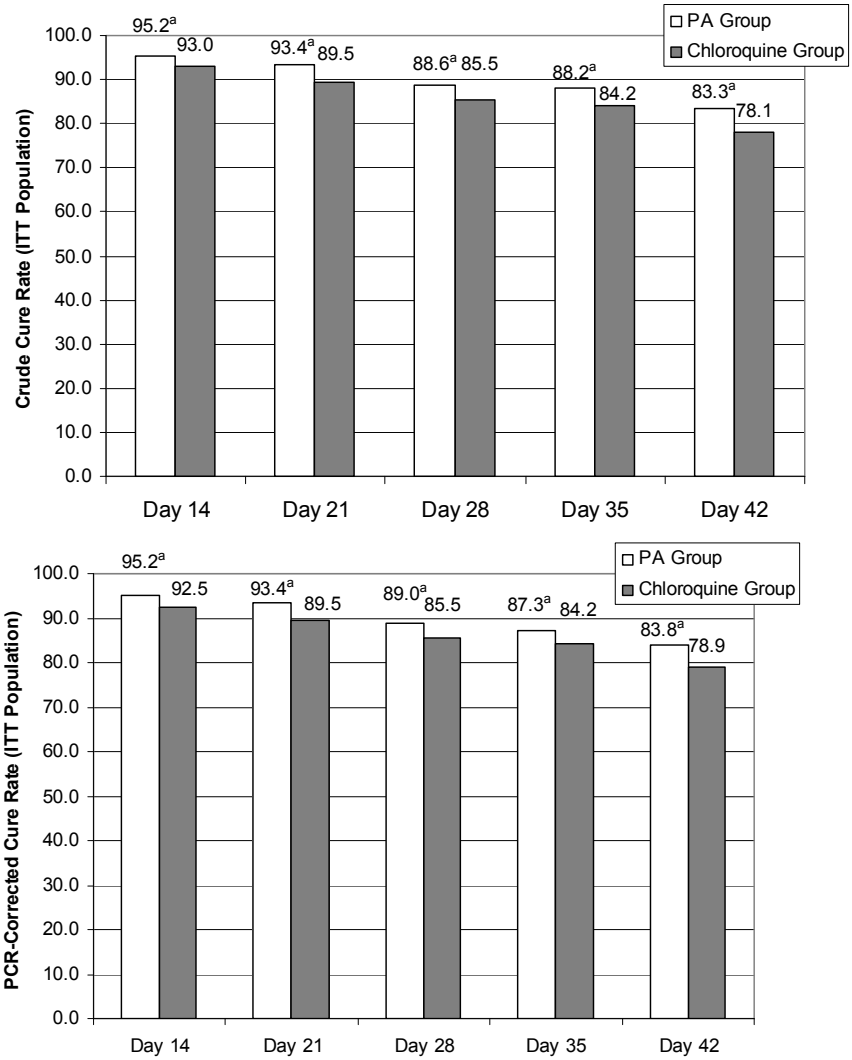
baseline *P. vivax* count, previous malaria infection, and amount of drug dosing) differences in Day 14 crude cure rate were observed.

**Figure 11. - Days 14, 21, 28, 35, and 42 Cure Rate – EE and Exploratory EE Populations**




Note: The Day 35 analysis was performed post hoc.
a - Non-inferiority of PA to chloroquine was concluded because the lower limit of the 2-sided 95% CI for the difference was >-10%.

**Figure 12. Days 14, 21, 28, 35, and 42 Cure Rate – ITT Population**




Note: The Day 35 analysis was performed post hoc.

a. Non-inferiority of PA to chloroquine was concluded because the lower limit of the 2-sided 95% CI for the difference was >-10%.

The non-inferiority of pyronaridine /artesunate compared with chloroquine was also demonstrated for the exploratory PCR-corrected cure rate (100.0% PA, 99.5% chloroquine) on Day 14. 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 were and are still not fully validated.

Pyronaridine /artesunate and chloroquine were both rapidly effective. *P. vivax* parasite count decreased rapidly (during the first 16 hours) in both the pyronaridine /artesunate

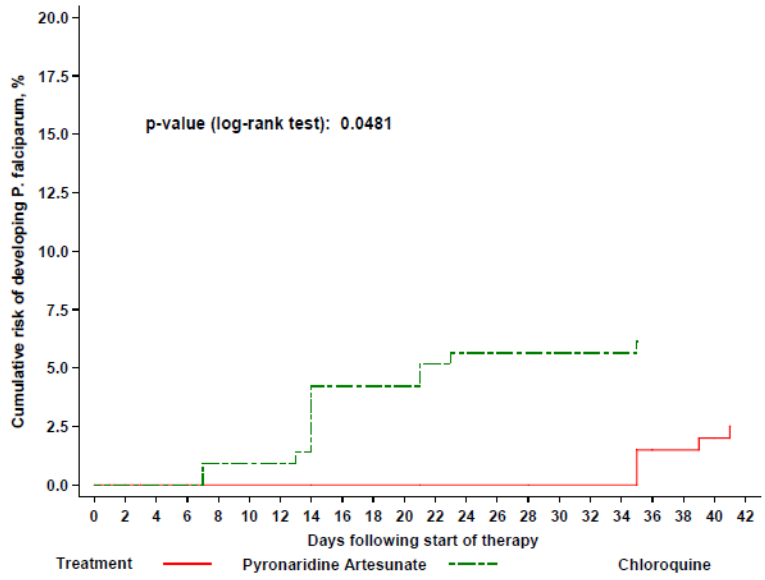
and chloroquine groups. Time to parasite clearance was statistically significantly ($p<0.0001$) shorter in the pyronaridine /artesunate group compared with the chloroquine group. A greater percentage of pyronaridine /artesunate subjects vs. chloroquine subjects achieved parasite clearance 24 hours (71.6% vs. 30.6%) and 48 hours (99.5% vs. 88.0%) after the first dose.

The clinical efficacy of the artemisinin derivatives is characterised by an almost immediate onset and rapid reduction of parasitaemia (deVries *et al*, 1996). The shorter times to parasite clearance and fever clearance with pyronaridine /artesunate treatment were expected, as studies of AS monotherapy for *P. vivax* infection have demonstrated rapid clearance of fever and parasites (Batty *et al*, 1998a; Pukrittayakamee *et al*, 2000; Hamedi *et al*, 2004).

Time to fever clearance was statistically significantly ($p<0.0071$) shorter in the pyronaridine /artesunate group compared with the chloroquine group (medians: 15.8 vs. 23.8 hours).

Risk of infection with *P. falciparum* was statistically significantly lower ($p=0.0481$) with pyronaridine /artesunate than with chloroquine, based on Kaplan-Meier estimates (Figure 13). The lower risk of infection with pyronaridine /artesunate compared with chloroquine may be due to the increased resistance of *P. falciparum* to chloroquine (Fu and Xiao, 1991; Chen *et al*, 1992).

**Figure 13. - Kaplan-Meier Estimates of P. falciparum Infection Rate – ITT Population**




The results of this study suggest that pyronaridine / artesunate is well suited to be used as an anti-malarial drug in areas where mixed infections occur.

Phase III comparative study of paediatric pyronaridine /artesunate granules with artemether Lumefantrine (Coartem) crushed tablets in infants and children with *P.falciparum* malaria

The main objectives of this Phase III comparative, open-labelled, randomised, multi-centre clinical study were to demonstrate the efficacy of a fixed combination of pyronaridine / artesunate granule formulation (60:20 mg), by showing a polymerase chain reaction (PCR)-corrected adequate clinical and parasitological cure rate of more than 90%, and to compare the efficacy (non-inferiority) and safety of pyronaridine /artesunate granule formulation with that of *Coartem*® (ie, the combination of artemether/lumefantrine [AL]) crushed tablets in a paediatric population; and also to assess the safety of pyronaridine /artesunate granule formulation in infants and children subjects with acute, uncomplicated *P. falciparum* malaria .

The study was conducted in a total of 535 infant and children subjects (≤12 years of age) suffering from acute, uncomplicated *P. falciparum* malaria, recruited from 7 sites in Burkina Faso, the Democratic Republic of Congo, Gabon, Ivory Coast, Kenya, Mali, and The Philippines. Subjects were randomised in a 2:1 ratio to receive either oral pyronaridine /artesunate (60:20-mg granules in 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). For pyronaridine /artesunate, the actual range covered by this regimen was 7.0:2.3 mg to 13.3:4.4 mg. Posology was based on body weight ranges for the pyronaridine /artesunate and AL regimens. Depending on body weight and randomisation, subjects received between 1 and 3 sachets of pyronaridine /artesunate granules or 1 or 2 crushed tablets twice a day of AL.

Subjects were followed for 42 days, with the primary efficacy end point occurring 28 days after initiation of study drug administration (Day 28). Subjects were confined to the study facility for ≥ 4 days (Days 0, 1, 2 and 3) and ideally remained in the vicinity of the study site for ≥ 7 days or when fever and parasite had been cleared for ≥ 24 hours, whichever occurred earlier. The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

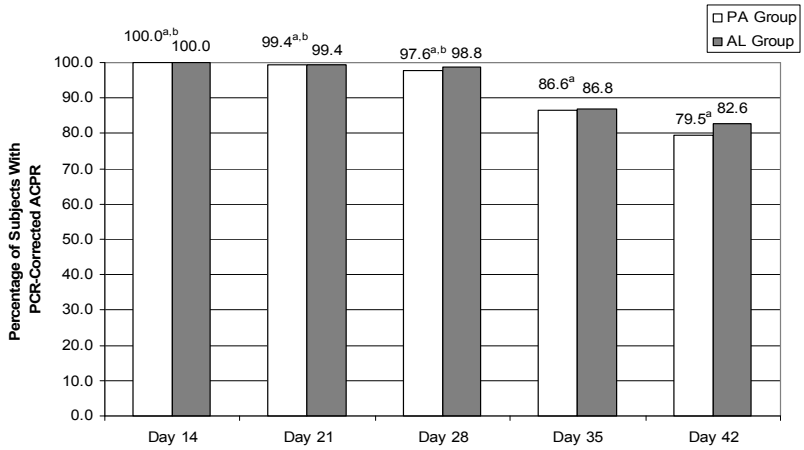
A total of 355 and 180 subjects were randomised to the pyronaridine /artesunate and AL treatment groups, respectively. There were approximately equal percentages of male and female subjects and most subjects were Black (96.1%) and between 5 and 12 years of age. The majority of subjects completed treatment (97.8%) and completed the study (77.8%). The most common reason for withdrawing from the study was *P. falciparum* parasite re-appearance.

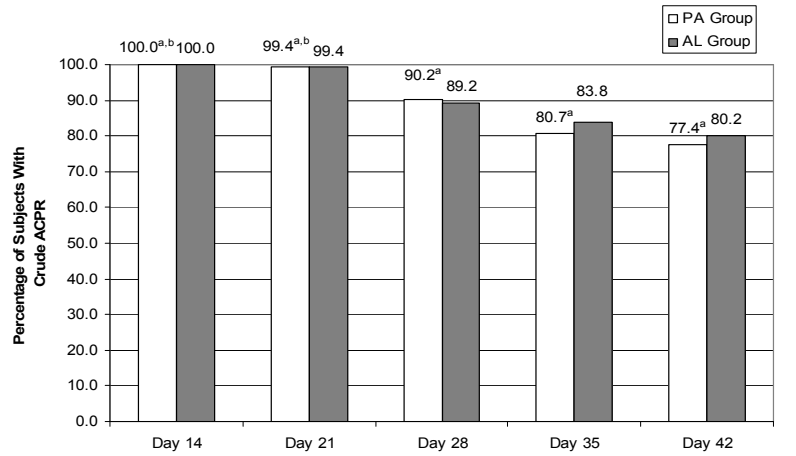
**Efficacy analysis**

For the primary end point, the PCR-corrected ACPR on Day 28 was statistically significantly >90% in the pyronaridine /artesunate group (97.6%) by the exact binomial test, and was demonstrated to be non-inferior to the PCR-corrected ACPR in the AL group (98.8%) (Figures 14 and 15). PCR-corrected ACPR was also statistically

significantly >90% (ie, >97%) in the pyronaridine /artesunate treatment group on Days 14 and 21. Non-inferiority of pyronaridine /artesunate to AL was concluded at each time point in both EE and ITT populations. A similar pattern of results was observed for crude ACPR. No clinically important subgroup (region, age, gender, previous malaria infection, and dose of study drug) differences in Day 28 PCR-corrected ACPR were observed.

**Figure 14. - Days 14, 21, 28, 35, and 42 ACPR – EE Population**



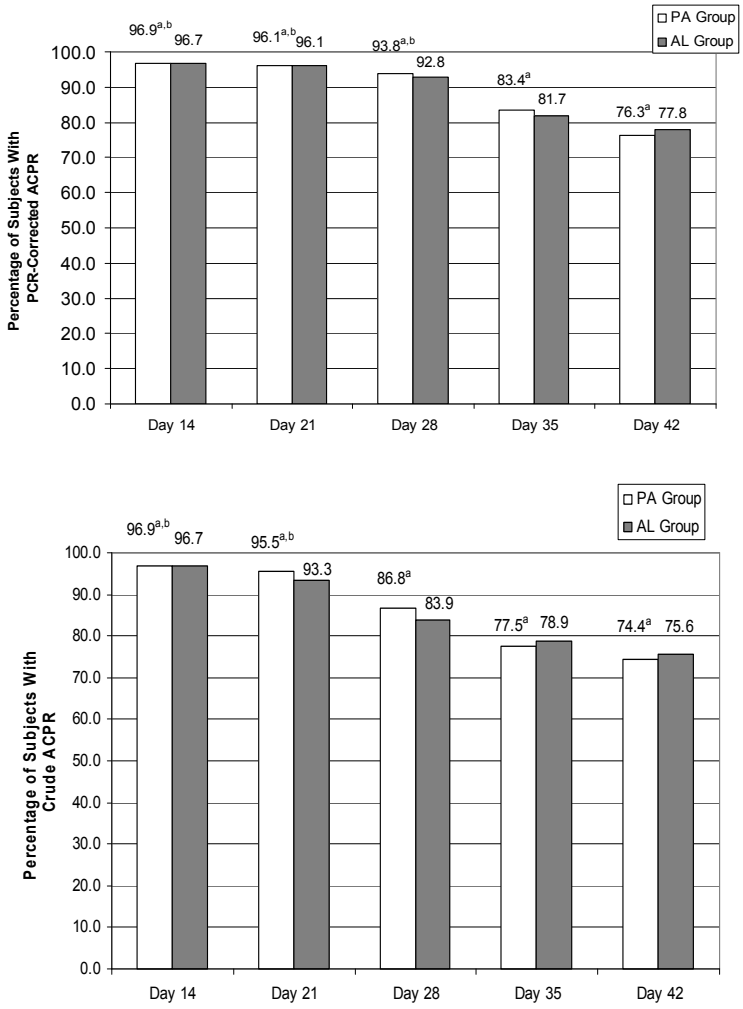




Note: The Day 21 and Day 35 analyses were performed post hoc.

a. Non-inferiority of PA to AL was concluded because the lower limit of the 2-sided 95% CI for the difference was >-10%.

b. The hypothesis that the ACPR in the PA group is ≤90% was rejected because the p-value associated with the 1-sided test was ≤0.025.

**Figure 15. - Days 14, 21, 28, 35, and 42 ACPR – ITT Population**




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 >-10%.

b. The hypothesis that the ACPR in the PA group is ≤90% was rejected because the p-value associated with the 1-sided test was ≤0.025.

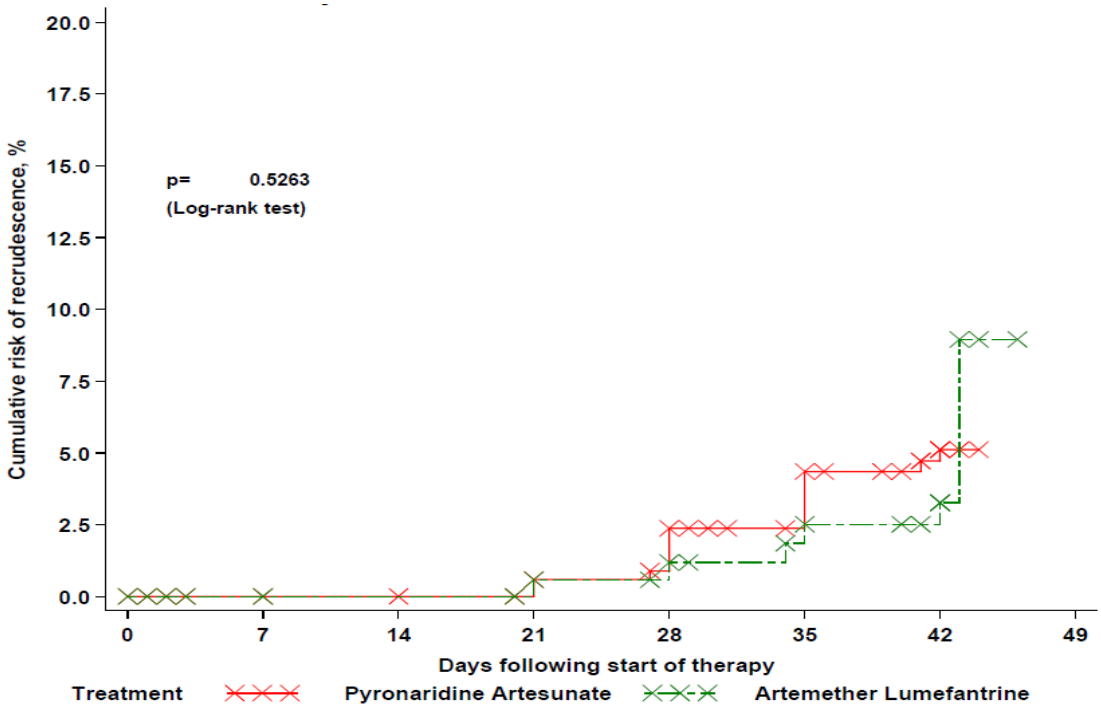
Pyronaridine /artesunate were rapidly effective. Parasite count decreased rapidly (during the first 16 hours) in both the pyronaridine /artesunate and AL groups. This was not unexpected as the clinical efficacy of the artemisinin derivatives is characterised by an almost immediate onset and rapid reduction of parasitaemia (de Vries *et al,* 1996). Time to parasite clearance was slightly statistically significantly (p=0.0459) shorter in the pyronaridine /artesunate group compared with the AL group. A greater percentage of

pyronaridine /artesunate subjects vs. AL subjects achieved parasite clearance 24 hours after the first dose (49.9% vs. 43.7%).

Time to fever clearance was similar in the pyronaridine /artesunate and AL groups.

No statistically significant difference between the pyronaridine /artesunate and AL groups was observed for the Kaplan-Meier estimates of new infection (p=0.7740), recrudescence (p=0.5263) (Figure 16), or parasite re-appearance (p=0.9800), as determined by PCR analysis.. However, among ITT subjects, a greater percentage of AL than pyronaridine /artesunate subjects (2.8% vs. 0.6%) was treatment failures in the PCR-corrected ACPR analysis due to new infection before Day 28.

**Figure 16. Kaplan-Meier Estimates of Recrudescence Rate – ITT Population**




## Immunity statement

Immunity can play an important part of how patients respond to malaria treatment. In the pyronaridine /artesunate clinical studies there was mixture of patients from Asia and Africa, children and adults and previous experience with malaria. Patients who were Asian had slower parasite and fever clearance time when compared to Africans. Recrudescence rate were lower for Africans compared with Asians and for adults compared with children. Recrudescence rates for patients who had no previous episodes of malaria were higher. These differences although not statistically significant point out the effect of immunity on outcomes in the pyronaridine /artesunate studies, but overall

pyronaridine /artesunate showed excellent activity against malaria in patients with immunity and those with out immunity.

***Conclusions on the overall comparative efficacy of pyronaridine / artesunate tablets and granules***

In the present Phase III studies, pyronaridine : artesunate fixed combination was shown to have good efficacy, safety and tolerability profiles in children and adults patients for the treatment of acute, uncomplicated *P. falciparum* or *P. vivax* malaria in Africa and South East Asia.

Pyronaridine /artesunate was shown to be at least as effective as mefloquine+artesunate and artemether /lumefantrine (for both tablet and granule formulations) for the treatment of patients with acute, uncomplicated *P. falciparum* malaria and also at least as effective as chloroquine for the treatment of subjects with acute *P. vivax* malaria.

The comparative studies consistently demonstrated greater efficacy rate compared to the 2006 WHO limit of 95% of PCR corrected ACPR level.

# 11. SUMMARY OF COMPARATIVE EVIDENCE ON SAFETY

## 11.1 Safety and tolerability

***Overview of Safety***

Extent of Exposure and Disposition

Approximately 3000 subjects received pyronaridine /artesunate across the completed Phase I, Phase II, and Phase III studies.

Safety was assessed in these studies by physical examinations, adverse events (AEs), vital signs, laboratory assessments (haematology, biochemistry, urinalysis), clinical signs and symptoms, and 12-lead electrocardiogram (ECG). The main adverse events observed in the pyronaridine / artesunate group included headache, cough, abdominal pain, vomiting and nausea. Vomiting was the most common adverse events leading to study drug discontinuation and withdrawal from the studies.

Common Adverse Events

Treatment-emergent adverse events reported for ≥5.0% of subjects in any treatment group across all Pyronaridine / Artesunate Phase II/III studies were

- headache (10.6%) and cough (5.9%) in the pyronaridine / artesunate group;
- headache (10.4%) and dizziness (6.6%) in the MQ + AS group;
- cough (9.1%), headache (7.6%), abdominal pain (5.1%), and upper respiratory tract infection (5.1%) in the AL group;
- headache (14.9%) and myalgia (9.2%) in the chloroquine group;
- headache (9.9%) and cough (5.6%) in all comparators combined

Differences in incidence of ≥5.0% between the pyronaridine / artesunate group and any of the other treatment groups were observed for dizziness (6.6% MQ + AS vs. 1.4% PA) and myalgia (9.2% chloroquine vs. 3.8% PA).

Deaths, Other Serious Adverse Events, and Adverse Events Leading to Premature Discontinuation

No subject died in the pyronaridine /artesunate clinical programme.

In the All Phase II/III Studies Population, the percentage of subjects with treatment-emergent serious adverse events ranged from 0.0% (chloroquine group) to 0.7% (MQ + AS group) across treatment groups and was 0.6% in the pyronaridine / artesunate group

Serious adverse events experienced by >1 subject in any treatment group were pyrexia

(2 subjects), malaria (2 subjects), typhoid fever (2 subjects), and urinary tract infection (2 subjects) in the pyronaridine /artesunate group and cerebral malaria in the all comparators group (1 MQ + AS, 1 AL).

Only 4 serious adverse events in 3 subjects in the All Phase II/III Studies Population were considered by the Investigator to be at least possibly related to study drug: hepatic enzyme increased and abortion incomplete in a pyronaridine /artesunate subject (12+4 mg/kg) in a Phase II study (SP-C-002-05) and convulsion and grand mal convulsion in 2 MQ + AS subjects, respectively, in a Phase III study (SP-C-004-06).

In the All Phase II/III Studies Population, the percentage of subjects with treatment-emergent adverse events leading to study drug discontinuation ranged from 0.9% (chloroquine and MQ + AS groups) to 1.3% (AL group) across treatment groups and was 1.1% in the pyronaridine /artesunate group. The most common treatment-emergent adverse events leading to study drug discontinuation in each treatment group was vomiting (range: 0.7-1.2%).

Clinical Laboratory and Other Observations Related to Safety

Changes in haematology parameters were generally of similar magnitude across comparative treatment groups of pyronaridine /artesunate, MQ + AS, AL, and chloroquine treatment groups and are expected consequences of malaria infection and treatment. [Camacho, 1998; Looareesuwan, 1987; van Vugt, 1998; Hutagalung, 2005; Borrmann, 2005; Erhart, 2004; Davis, 1991; Camacho, 1999] A transient decrease in mean haemoglobin levels that peaked on Day 7 was observed in all treatment groups, an effect that was greater in the pyronaridine / artesunate and MQ + AS groups than in the AL and chloroquine groups. Falls in haemoglobin are common after effective treatment with a variety of anti-malarial drugs and so the findings in the studies are as expected.

Overall, pyronaridine /artesunate treatment was associated with transient alanine aminotransferase (ALT) elevations in a small subset of subjects. The early onset (Day 3-7) and rapid resolution are consistent with a direct, low-level toxicity. Serious idiosyncratic hepatotoxicity typically begins weeks or months after starting therapy. These observations, combined with the fact that pyronaridine /artesunate is dosed for only 3 days, indicate that the risk of progressive liver injury to subjects treated with pyronaridine /artesunate is small. These findings were supported by a rigorous review by an independent safety monitoring board that included 3 expert hepatologists.

No unexpected or clinically concerning results were observed in the analysis of adverse events and potentially clinically significant laboratory values by intrinsic factors (age group, gender, race, weight), disease severity factors (previous malaria episode, number of previous malaria episodes in the last 12 months, baseline parasitaemia), or extrinsic factors (region, study drug dose).

Mean decreases in heart rate were observed in all treatment groups, a finding that has

been observed in other studies of malaria treatment. [Ribeiro, 1998; Karbwang, 1992; Karbwang, 1994; Sowunmi, 1996] Bradycardia was recorded as an adverse event for 1.1% of pyronaridine /artesunate subjects and 0.8% of AL subjects. The mean age of the subjects was 15 to 27 years across treatment groups. In relatively fit youths, a slow heart rate is not uncommon. Once the pyrexia of malaria, with its associated tachycardia, has been cleared, a slowing of the heart may suggest that treatment has resulted in the patient returning to his or her normal low heart rate.

Electrocardiogram findings of any significant abnormalities were low and do not suggest a safety concern with pyronaridine /artesunate treatment. QT was specifically measured in Phase I and in Phase II/III a review of QT was conducted for those subjects with adverse events identified in ICH Topic E14 as being those of particular risk for association with a prolonged QT. The conclusion of this detailed work is that pyronaridine / artesunate does not exhibit a potential to prolong QT/QTc.

The overall pattern of safety findings in subjects with a higher baseline parasitaemia did not appear to be associated with a different profile from that seen in the subject population as a whole.

***Conclusions on Safety from Phase II/III***

- Pyronaridine / artesunate and the comparator drugs (AL, MQ + AS, chloroquine) were well tolerated. The adverse event profiles of pyronaridine /artesunate and the comparator drugs were similar and consistent with those previously reported for pyronaridine, artemisinins, AL, MQ, and chloroquine
- Changes in haematology parameters were generally of similar magnitude in all treatment groups and are expected consequences of malaria infection and treatment.
- Pyronaridine / artesunate treatment was associated with transient ALT elevations in a small number of subjects. The early onset (Day 3-7) and rapid resolution are consistent with a direct, low-level toxicity and do not indicate a risk of progressive liver injury with 3-day pyronaridine / artesunate treatment.
- Other biochemistry laboratory observations, also expected consequences of malaria infection and treatment, were generally similar across treatment groups.
- No unexpected or clinically concerning results were observed in the analysis of adverse and laboratory values by intrinsic factors (age group, gender, race, weight), disease severity factors (previous malaria episode, number of previous malaria episodes in the last 12 months, baseline parasitaemia), or extrinsic factors (region, study drug dose).
- Mean decreases in heart rate were observed in all treatment groups, a finding that has been observed in other studies of malaria treatment. This is not unexpected in subjects who are responding to therapy and becoming afebrile.
- Electrocardiogram results do not suggest a safety concern with pyronaridine / artesunate treatment.

## 11.2 A Risk Management Plan for pyronaridine artesunate fixed-dose combination

RISK MANAGEMENT PLAN

- Routine pharmacovigilance for individual adverse reactions related to potential interactions (potentiation of effect)
- Literature review for reports of interactions with components of PYRAMAX
- A pregnancy register will be set up to monitor the outcomes of pregnancies of women who are or become pregnant at the time of receiving PYRAMAX
- Routine pharmacovigilance for individual case reports
- Routine pharmacovigilance for adverse reactions related to repeat dosing
- A longitudinal study is to be undertaken with repeat doses of PYRAMAX over a two-year period

## 11.3 Use in pregnancy and lactation

**Pregnancy**
The safety of pyronaridine tetraphosphate and artesunate when administered concurrently for use in human pregnancy has not been established and the potential risk is unknown.

A component of Pyramax is artesunate, a recognized *in vivo* embryotoxic and teratogenic compound in animal models, including primate. No controlled studies have been conducted to assess the effects in human pregnancy.

Artemisinin compounds cannot be recommended for treatment of malaria in the first trimester of pregnancy. However, they should not be withheld if treatment is considered lifesaving for the mother and other antimalarials are considered unsuitable. Because of the limited safety data, artemisinin compounds should only be used in the second and third trimesters of pregnancy when other treatments are considered unsuitable.

**Lactation**
It is not known whether artesunate or pyronaridine are excreted in human milk. Where possible, women taking Pyramax should not breast feed during treatment.

## 11.4 Drug interactions

To date no drug-drug interaction studies have been completed however an interaction study with Pyramax and ritonavir is ongoing

Pyronaridine is an *in vitro* inhibitor of CYP2D6. This may be of clinical relevance for compounds with a low therapeutic index and caution is advised when co-administering Pyramax with drugs that are metabolised by CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitryptyline, clomipramine)

# 12. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST - EFFECTIVENESS WITHIN THE PHARMACOLOGICAL CLASS OR THERAPEUTIC GROUP

(Currency : U$)

<table>
<tr><th rowspan="2">WT</th><th colspan="2">PY+AS</th><th rowspan="2">Price</th><th>AL</th><th>Price</th><th>ASAQ</th><th>Price</th></tr>
<tr><th>Granule</th><th>Tablet</th><th></th><th></th><th></th><th></th></tr>
<tr><td>5<10</td><td>1 x 3 sachet AS 20mg</td><td></td><td>0.252</td><td rowspan="2">5<WT<15 Disp 6 tablet AS 20mg</td><td rowspan="2">0.37</td><td rowspan="2"><8.9Kg 3 tablet AS 25mg</td><td rowspan="2">0.30</td></tr>
<tr><td>10<15</td><td>2x3 sachet</td><td></td><td>0.504</td></tr>
<tr><td>15<20</td><td>3x3 sachet</td><td rowspan="3">1x3 tablet AS 60mg“</td><td>Sac 0.756 Tab 0.545</td><td rowspan="3">15<WT<25 Disp 12 tablet AS 20mg</td><td rowspan="3">0.74</td><td rowspan="2">9<WT<18 3 tablet AS 50mg</td><td rowspan="2">0.39</td></tr>
<tr><td>20<25</td><td>4x3 sachet</td><td>Sac 1.008 Tab 0.545</td></tr>
<tr><td>25<30</td><td rowspan="4"></td><td rowspan="2">1.089</td><td rowspan="2">25<WT<35 18 tablet AS 20mg“</td><td rowspan="2">1.11</td><td rowspan="3">18<WT<36 3 tablet AS 100mg</td><td rowspan="3">0.59</td></tr>
<tr><td>30<35</td></tr>
<tr><td>35<40</td><td rowspan="3">35<WT 24 tablet AS 20mg</td><td rowspan="3">1.40</td></tr>
<tr><td>40<45</td><td rowspan="4">3x3 tablet AS 60mg</td><td rowspan="3">1.635</td><td rowspan="2">36<WT 6 tablet AS 100mg“</td><td rowspan="2">1.00</td></tr>
<tr><td>45<50</td></tr>
<tr><td>50<55</td><td rowspan="3">5<WT<15 Disp 6 tablet AS 20mg</td><td rowspan="3">0.37</td><td rowspan="2"><8.9Kg 3 tablet AS 25mg</td><td rowspan="2">0.30</td></tr>
<tr><td>55<60</td></tr>
<tr><td>60<65</td><td rowspan="2">9<WT<18 3 tablet AS 50mg</td><td rowspan="2">0.39</td></tr>
<tr><td>65≤ WT</td><td>4x3 tablet AS 60mg</td><td>2.18</td><td>15<WT<25 Disp 12 tablet AS 20mg</td><td>0.74</td></tr>
</table>

- Each price is U$ xxx per treatment in different weight band.
- AL: artemethur/lumefantrine, ASAQ:artesunate/amodiaquine, WT: body weight
- Bench mark price : Coartem of Norvatis, Coarsucam/Winthrop of sanofi aventis
- Price information of other ACTs :
  http://www.theglobalfund.org/programs/amfm/report.aspx

# 13. SUMMARY OF REGULATORY STATUS OF THE MEDICINE (IN COUNTRY OF ORIGIN, AND PREFERABLY IN OTHER COUNTRIES AS WELL)

In the fixed dose combination of pyronaridine /artesunate, the registration file for tablets was first submitted to EMA on April 1, 2010 for obtaining a Scientific Opinion according to Article 58 of Regulation (EC) 726/2004.

EMA representative inspected GCP compliance at sponsor site during Sep. 27 to Oct. 1, 2010 and two clinical trial sites in Thailand and Kenya for each one week in October, 2010. The review result of EMA for GCP compliance will be available on the 2$^{nd}$ week of December, 2010. On the other hands, EMA is scheduled to inspect GMP compliance during Jan. 17-21, 2011 at producer site.

The NDA application to Korean-FDA was submitted August 18, 2010. Representative of Korean-FDA inspected GMP compliance for the Finished Dosage Form(FDF) production facilities on Oct. 20-21 and it will inspect again for the Active Pharmaceutical Ingredients(API) production facilities on Nov. 25-26, 2010.

# 14. AVAILABILITY OF PHARMACEUTICAL STANDARDS

Artesunate standards:
- WHO (International Pharmacopoeia, Volume X, 4th edition, 2006),
- US Pharmacopoeia.
- In house Standard harmonised with International Pharmacopoeia.

Pyronaridine standards:
- Chinese Pharmacopoeia.
- In house Standard.

Fixed dose combination:
- In house standard

# 15. PROPOSED TEXT FOR THE WHO MODEL FORMULARY

## 15.1 NAME OF THE MEDICINAL PRODUCT

Pyramax 180 mg/60 mg Film Coated Tablets

Pyramax 60 mg/20 mg Granules in sachet

## 15.2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Pyramax tablet contains 180 mg Pyronaridine tetraphosphate and 60 mg Artesunate.

Each Pyramax granule sachet contains 60 mg Pyronaridine tetraphosphate and 20 mg Artesunate.

## 15.3 PHARMACEUTICAL FORM

TABLETS:
Film coated tablets. Round, biconvex, orange coloured tablets.

GRANULES:

Orange coloured, mixture of powder and granules.

## 15.4 Clinical particulars

### *15.4.1 Therapeutic indications*

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 granules are indicated for the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* in patients weighing 5 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.

### *15.4.2 Posology and method of administration*

*Method of administration*

The dose should be taken orally once a day for three days.
Pyramax tablets and granules 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.

TREATMENT

*Dosage in adults, children and infants*
Pyramax tablets should be taken orally as a single daily dose for three consecutive days.

**TABLETS**

| Body weight / Number of tablets | | 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 |

**GRANULES**

Body weight / Number of granule sachets

| Body weight | Number of granule sachets | Regimen |
|---|---|---|
| 5 - < 8 kg | 1 sachet | Daily for 3 days |
| 8 - < 15 kg | 2 sachets | Daily for 3 days |
| 15 - < 20 kg | 3 sachets | Daily for 3 days |
| 20 - < 25 kg | 4 sachets | Daily for 3 days |

Dosage in paediatrics
Pyramax is dosed according to body weight for both tablets and granules and is suitable for children and infants in the weight categories shown above. Pyramax tablets are not recommended for use in children below 5 kg body weight as safety and efficacy of Pyramax in children below 5 kg has not been established for the tablets.

*Dosage in the elderly*

There is no experience in patients over 65 years of age
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.

### *15.4.3 Contraindications*

Pyramax is contra-indicated in individuals with known hypersensitivity to pyronaridine or artesunate or any component of the formulation.

Pyramax tablets or granules should not be used to prevent malaria.

### *15.4.4 Special warnings and precautions for use*

Artemisinin compounds cannot be recommended for treatment of malaria in the first trimester of pregnancy. However, they should not be withheld if treatment is considered lifesaving for the mother and other antimalarials are considered unsuitable. Because of the limited safety data, artemisinin compounds should only be used in the second and third trimesters of pregnancy when other treatments are considered unsuitable.

The studies of Pyramax in the treatment of *P. falciparum* and *P. vivax* malaria were separate, and mixed infections were not allowed as an inclusion criterion. However, the efficacy of Pyramax against both of these parasites is such that it would be anticipated that mixed infections of *P. falciparum* and *P. vivax* would be cured by Pyramax alone. This would mean that the geographical reach of this agent would embrace both Africa and Asia comprehensively. There are no data on the potential for Pyramax to cure *P. ovale* and *P. malariae* infections but as these parasites are sensitive to chloroquine, and are also susceptible to amodiaquine, mefloquine and the artemisinin derivatives and there are data to show that they can be effectively treated with pyronaridine; it would be anticipated that Pyramax should be effective against these organisms as well.

Pyramax tablets have not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria, including hyperparasitaemia, pulmonary oedema or renal failure. Patients with severe malaria are not candidates for oral therapy with Pyramax.

The safety and effectiveness of Pyramax for the treatment of malaria in patients with HIV/AIDS has not been established. If Pyramax is used in these patients, the parasite load should be closely monitored.

In patients with acute malaria who present with severe diarrhoea and vomiting alternative therapy should be considered. If Pyramax is used in these patients, the parasite load should be closely monitored.

Pyramax should not be used as a prophylactic or as an emergency self-treatment for presumed acute malaria.

Pyramax is only a blood schizonticide and for the treatment of *P. vivax* malaria, a radical cure (to destroy the parasite in the liver and thus prevent relapse) is required with an hypnozoitocidal drug such as primaquine.

The safety and effectiveness of Pyramax tablets or granules for treatment of malaria in patients who weigh less than 5 kg has not been established.

The safety and effectiveness of Pyramax tablets for retreatment of malaria in patients previously treated with Pyramax has not been established.

In the event of proven recrudescent malaria infections after treatment with Pyramax, patients should be treated with a different blood schizonticide.

Patients should be closely monitored when receiving concurrent treatment with medications known to inhibit Cytochrome CYP3A4 and CYP2D6 such as HIV treatments, ketoconazole or herbal remedies as the effects on blood levels of Pyramax by agents that are metabolised through these pathways is not known.

### *15.4.5 Interaction with other medicinal products and other forms of interaction*

No interaction studies have been performed in humans.

Pyronaridine is an *in vitro* inhibitor of CYP2D6. This may be of clinical relevance for compounds with a low therapeutic index and caution is advised when co-administering Pyramax with drugs that are metabolised by CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitryptyline, clomipramine)

### *15.4.6 Fertility, pregnancy and lactation*

The safety of pyronaridine tetraphosphate and artesunate when administered concurrently for use in human pregnancy has not been established and the potential risk is unknown.

A component of Pyramax is artesunate, a recognized *in vivo* embryotoxic and teratogenic compound in animal models, including primate. No controlled studies have been conducted to assess the effects in human pregnancy.

Artemisinin compounds cannot be recommended for treatment of malaria in the first trimester of pregnancy. However, they should not be withheld if treatment is considered lifesaving for the mother and other antimalarials are considered unsuitable. Because of the limited safety data, artemisinin compounds should only be used in the second and third trimesters of pregnancy when other treatments are considered unsuitable.

**Lactation**
It is not known whether artesunate or pyronaridine are excreted in human milk. Where possible, women taking Pyramax should not breast feed during treatment.

### *15.4.7 Undesirable effects*

The safety of pyronaridine tetraphosphate and artesunate for treatment of malaria has been evaluated in more than 2800 patients.
The most commonly reported (≥1/100 to <1/10) adverse event were headache, eosinophilia, neutropenia, anaemia, increased platelet count, vomiting, abdominal pain, bradycardia, transaminase increases and hypoglycaemia.

The following table provides a summary of adverse reactions reported with Pyramax in clinical trial reports.

| System Organ Class | Common | Uncommon | Rare |
|---|---|---|---|
| **Blood and lymphatic system disorders** | Anaemia, eosinophilia, neutropenia,increased platelet count* | Basophilia, leukocytosis, leukopenia, lymphocytosis, monocytosis, splenomegaly, thrombocytopenia | Lymphopenia, pancytopenia |
| **Cardiac disorders** | Bradycardia | Palpitations, ventricular extrasystoles | Arrhythmia, atrioventricular block first degree, sinus arrhythmia |
| **Ear and labyrinth disorders** | | Vertigo | Ear pain, hearing impaired, tinnitus |
| **Eye disorders** | | | Conjunctivitis |
| **Gastrointestinal disorders** | Abdominal Pain, Vomiting | Constipation, Diarrhoea Dyspepsia, Gastritis, Nausea | Abdominal Tenderness, Aphthous Stomatitis, Stomach Discomfort, Tongue Ulceration |

| System Organ Class | Common | Uncommon | Rare |
|---|---|---|---|
| **General disorders and administration site conditions** | | Asthenia, fatigue | Chest pain, chills, hypothermia, pyrexia |
| **Hepatobiliary disorders** | | Hepatomegaly | Hepatosplenomegaly, liver tenderness |
| **Immune system disorders** | | | Hypersensitivity |
| **Infections and infestations** | | Gastroenteritis, malaria, oral herpes, respiratory tract infection, tinea capitis, upper respiratory tract infection, urinary tract infection | Bronchitis, bronchopneumonia, infection parasitic, pharyngitis, pharyngotonsillitis, *Plasmodium falciparum* infection, pneumonia, rhinitis, subcutaneous abscess, tracheobronchitis, wound |
| **Investigations** | Transaminases increased | Blood albumin decreased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine decreased, blood sodium increased, electrocardiogram abnormal, electrocardiogram QT prolonged, liver function test abnormal | Blood albumin increased, blood bilirubin decreased, blood bilirubin increased, blood creatinine increased, blood potassium decreased, haematocrit increased, red blood cell count increased, white blood cells urine |
| **Metabolism and nutrition disorders** | Hypoglycaemia | Anorexia, hyperkalaemia | Decreased appetite, hyperglycaemia |
| **Musculoskeletal and connective tissue disorders** | | Myalgia | Arthralgia, back pain |
| **Nervous system disorders** | Headache | Dizziness, Dysgeusia, Paraesthesia | Somnolence |
| **Pregnancy, puerperium and perinatal conditions** | | | Abortion complete |
| **Psychiatric disorders** | | Insomnia | Sleep talking |

| System Organ Class | Common | Uncommon | Rare |
|---|---|---|---|
| **Renal and urinary disorders** | | Haematuria, proteinuria | Ketonuria |
| **Reproductive system and breast disorders** | | | Vulvovaginal pruritus |
| **Respiratory, thoracic and mediastinal disorders** | | Cough | Asthma, epistaxis, haemoptysis, rhinorrhoea |
| **Skin and subcutaneous tissue disorders** | | Hyperhidrosis, pruritus, rash | Blister, dermatitis, urticaria papular |
| **Vascular disorders** | | | Hypertension, hypotension |

### *15.4.8 Overdose*

No case of overdosage with Pyramax has been reported. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, transaminases (AST and ALT) should be monitored.

## 15.5 PHARMACOLOGICAL PROPERTIES

### *15.5.1 Pharmacodynamic properties*

Pharmacotherapeutic group: *Artemisinin and derivatives, combinations*, ATC Code: P01BF06

*Mechanism of action*

Pyronaridine inhibits the formation of β-haematin thus, preventing the malarial parasite from neutralizing haem, which is toxic to the parasite. Additionally, by forming a drug-haematin complex pyronaridine inhibits glutathione-dependent degradation of haematin and enhances haematin-induced lysis of red blood cells. Both these actions lead to parasite death.
Several mechanisms of action have been proposed to account for the activity of artemisinins; the generation of free radicals inside the parasite food vacuole and inhibition of the parasite's sarcoplasmic endoplasmic reticulum calcium-ATPase are widely accepted.

*Pharmacodynamics effects*

Whilst the outcome of *in vitro* studies using combinations of pyronaridine and

artemisinin have reported mixed results, efficacy studies in rodent models of malaria using sensitive and resistant parasite strains have shown additive or synergistic effects using a combination of both compounds in a 3:1 ratio respectively.

Pyronaridine has potent *in vitro* activity against *P. falciparum* and *P. vivax* strains and clinical isolates including those resistant to other antimalarials. Against erythrocytic *P. falciparum* activity is greatest for the ring-form stage ($ED_{50}$s; 8.3 nM), followed by schizonts (11.6 nM) then trophozoites (14.0 nM). Pyronaridine retains high activity against chloroquine resistant strains. *In vivo* efficacy of pyronaridine has been reported in mouse and non-human primate models of malaria.

Artesunate and its active principal metabolite DHA show potent *in vitro* activity against multiple strains of *P. falciparum* and *P. vivax*, as well as against clinical isolates, including those resistant to other antimalarials. Reported $IC_{50}$s for inhibition of parasite multiplication are usually <10 ng/mL. *In vivo* efficacy of artesunate has been reported in mouse, rat and non-human primate models of malaria.

*Cross resistance*

Resistance to pyronaridine has not been reported. *In vivo* pyronaridine retains activity against chloroquine-resistant strains. It is established that pyronaridine is considerably more active than chloroquine against *P. falciparum in vitro* and retains high activity against the majority of chloroquine-resistant field isolates.

Cross resistance to other Mannich bases such as amodiaquine cannot be ruled out.

Resistance to artemisinin has been reported in clinical isolates in vitro and genetically stable resistance has been observed in animal models. However, generally, resistance has been reported as labile and difficult to induce experimentally. The threshold for resistance of *P. falciparum t*o artesunate remains indeterminate however, prolonged parasite clearance times in patients with apparent artemisinin resistance have recently been described in Western Cambodia.

*Clinical efficacy and safety*

Pyramax was demonstrated in Phase III studies to be at least as effective as artemether/lumefantrine and mefloquine + artesunate in the treatment of acute uncomplicated *P. falciparum* in 2280 children and adults for the primary endpoint of Polymerase chain reaction (PCR)-corrected adequate clinical and parasitological response (ACPR) at 28 days. Pyramax was rapidly effective, with more than 90% of subjects clearing parasites and fever within 48 hours. Parasite count (*P. falciparum* asexual forms) decreased rapidly (during the first 16 hours) in both the Pyramax and comparator groups. Time to parasite clearance was statistically significantly shorter in the Pyramax group compared with artemether/lumefantrine group based on the log-rank test. In the integrated analysis of all Phase III studies with *P. falciparum*, no clinically

important differences in PCR-corrected ACPR were observed by region, age, gender, race, weight, previous malaria episode, baseline parasitaemia, or formulation. Crude cure rate results were also similar. The median time to fever clearance was 15.5 hours.

In the study in subjects with *P. vivax* malaria, non-inferiority of Pyramax compared with chloroquine was demonstrated with respect to the crude cure rate on Day 14 in the efficacy evaluable population (in children and adults), which was the primary end point in that study. Results were maintained in the intent-to-treat population. A high crude cure rate (95.5%) was still observed at Day 42. Times to fever and parasite clearance were significantly shorter for Pyramax than chloroquine in this study. In addition, the risk of subsequent infection with *P. falciparum* was statistically significantly lower with Pyramax than with chloroquine.

Pyramax and the comparator drugs (artemether/lumefantrine, mefloquine + artesunate, chloroquine) were well tolerated during the clinical studies. The adverse event profiles were similar and consistent with those previously reported for pyronaridine tetraphosphate, artemisinins, artemether/lumefantrine, mefloquine and chloroquine.

Changes in haematology parameters were generally of similar magnitude in all treatment groups and are expected consequences of malaria infection and treatment. Pyramax treatment was associated with mostly mild transient ALT elevations, with elevations of >3x upper limit of normal in a small number of subjects. The early onset (Day 3-7) and rapid resolution are consistent with a direct, low-level toxicity. Other biochemistry laboratory observations, also expected consequences of malaria infection and treatment, were generally similar across treatment groups.
Mean decreases in heart rate were observed in all treatment groups and corresponded to reduction in the fever associated with the malaria infection.
Electrocardiogram results do not suggest a safety concern with treatment and Pyramax does not appear to have a potential to prolong QT interval.
No unexpected or clinically significant results were observed in the analysis of AEs and laboratory values by intrinsic factors (age group, gender, race, weight), extrinsic factors (region, study drug dose) or disease severity factors (previous malaria episode, number of previous malaria episodes in the last 12 months, baseline parasitaemia) and in particular, patients with higher parasite loads (≥80.000/µL) were not at greater risk of adverse events, laboratory changes or electrocardiogram and cardiac events than the main population as a whole.

### *15.5.2 Pharmacokinetic properties*

There is no pharmacokinetic interaction between pyronaridine tetraphosphate and artesunate at the recommended dose.

In clinical trials trough levels of pyronaridine and artesunate in children were generally within the range observed in adults.

*Absorption*

Following administration of Pyramax tablets to healthy volunteers and patients with malaria, peak plasma concentrations are generally reached between 0.5 and 1.0 hours post-dose for artesunate, between 1 and 2 hours post-dose for DHA and between 2 and 8 hours post-dose for pyronaridine.
Exposure to artesunate and pyronaridine was increased by 34% and 20% respectively when Pyramax was administered with a high fat meal, however these effects were not judged clinically significant and patients can take Pyramax tablets without regard to meals

*Distribution*

Pyronaridine and its metabolites are extensively distributed into tissues, with highest concentrations achieved in the liver, spleen, adrenal gland, kidney and thyroid gland in the rat. There is evidence that pyronaridine binds to melanin in the eye. In the dog, approximately 10% of a single dose of pyronaridine remained in the liver 10 months after administration.
Pyronaridine preferentially associates with blood cells, exhibiting a whole blood:plasma concentration ratio of approximately 1.5:1. Pyronaridine is highly bound to human serum proteins *in vitro* (92 to 95%).

Artesunate and its metabolites are primarily associated in the rat with tissues involved in absorption and excretion and high levels were also found in the spleen.
Plasma protein binding of artesunate and DHA is moderate (62 to 93%) and albumin is the principal binding protein for DHA in human plasma.

*Biotransformation*

Pyronaridine appears to have a large number of potential metabolites, with no clear major metabolic route. In rat and dog pyronaridine was largely excreted unchanged. *In vitro* experiments indicate that CYP1A2, CYP2D6 and CYP3A4 could be involved in the metabolism of pyronaridine. *In vitro,* pyronaridine inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Artesunate is very rapidly metabolized by esterases to the active metabolite dihydroartemisinin (DHA). DHA is subsequently conjugated with glucuronic acid via UGT1A9 and UGT2B7.

*Elimination*

Pyronaridine is eliminated slowly from blood, with an elimination half-life of between 14 and 18 days. Urinary excretion of unchanged pyronaridine is <1% in healthy human subjects.

In patients with uncomplicated malaria, artesunate and DHA are cleared from plasma with an elimination half-life of about 0.5 and 0.8 hours, respectively. No urinary excretion data are available for humans.

*Hepatic and Renal Impairment*

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment

*Elderly Patients*

No specific pharmacokinetic studies have been performed in patients older than 65 years of age.

### *15.5.3 Preclinical safety data*

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, genotoxicity, phototoxicity, local tolerance or single dose toxicity.

Non- clinical data revealed the following effects which may have clinical relevance:

*Repeat-dose Toxicity*

Studies were initially performed with daily dosing for up to 28 days however, based on the clinical regime of 3 consecutive days dosing only, subsequent cyclical repeat dose toxicity studies were performed to better reflect clinical use. Four cycles were administered with each cycle comprising 3 consecutive days dosing followed by 4 days of non-treatment. Repeat dosing, whether daily or cyclic, produced excessive and long-lasting tissue and systemic exposure compared to the intended clinical regimen (a single cycle of 3 doses). In order to provide toxicology data with direct relevance to the single-cycle clinical dosing regimen, single-cycle studies in rat and dog are on-going. These studies are investigating the longevity and reversibility of effects following a single 3-day cycle of pyronaridine tetraphosphate and artesunate (3:1) in both rat and dog and data up to 25 days after a single-cycle in dogs is included in this document.

Repeat-dose toxicity studies with Pyramax in rats and dogs produced similar effects to those seen with each component individually

The predominant feature in animals receiving repeated higher doses of pyronaridine tetraphosphate:artesunate (3:1) was widespread yellow discolouration of tissues and organs seen in-life as yellow skin, eyes, mucosal membranes and extremities, and

post-life in tissues and organs. This was due to accumulation of pyronaridine and the incidence and intensity of the discolouration was related both to dose level and to the number of doses administered. For example, it was typically seen following a single cycle at the highest doses in rat (≥150:50 mg/kg/dose) but not following 4 cycles at lower doses in rat (60:20 mg/kg/dose).

Microscopically, after repeated dosing, this was seen as a widespread accumulation of basophilic material in many tissues and organs, sometimes present without associated inflammatory change (as for bone marrow and eye) but more often associated with dose-related inflammatory changes (as for liver, lung, spleen, gall bladder and kidney). It should be noted that, following a single cycle of treatment in dog, inflammatory changes were confined to liver and brain.

These inflammatory changes are considered secondary to the body's attempt to clear the accumulated material, and an increase in white blood cell count, predominantly in neutrophils and monocytes, is also considered a sequalae of these changes. In more reactive tissues, notably rat liver, inflammatory and degenerate changes worsened over time in response to the prolonged presence of material, and this was correlated with increasing transaminase levels. This was not seen in dog. Liver necrosis was not seen in either species and bilirubin levels were largely unaffected.

Minimal to mild perivasculitis of the brain was noted in all repeat dose dog studies, including the single cycle study. This occurred with dose-related incidence and was fully reversible. Brain changes in rat were of a different nature (basophilic vacuolated macrophages in the choroid plexus) and were also fully reversible. No neurobehavioural changes were noted in either species and it should be noted that these changes are considered entirely unrelated to the reported neurotoxicity seen in laboratory animals following prolonged exposure to some artemisinins.

*Reproductive toxicity*

Neither pyronaridine nor artesunate have any effects on rat male fertility.

Artesunate is embryolethal at varying maternal dose levels and dosing regimens, depending on the nonclinical species. Together with most other artemisinins (dihydroartesunate, arteether, artemether) artesunate acts by depleting embryonic erythroblasts leading to severe anaemia.

Pyronaridine results in maternal toxicity but there was no evidence of teratogenicity.

*Carcinogenicity*

Carcinogenicity studies were not conducted since the treatment is limited to 3 days.

## 15.4 Shelf life

18 months

## 15.5 Special precautions for storage

Store below 30°C.
Store in the original package. Protect from light.

## 15.6 Nature and contents of container

For tablet ;
Tropical PVC/aluminium foil blisters containing 9 tablets.
The blisters are packed into cartons containing one or 10 blisters
.
For granule ;
9 stick pack sachets are packed into one pillow pack in a carton.

**Special precautions for disposal <and other handling>**
No special requirements.

**MARKETING AUTHORISATION HOLDER**
Shin Poong Pharmaceutical Co., Ltd
748-31 Yoksam-Dong
Gangnam-Gu
Seoul 135-925
Korea