19 November 2015
EMA/15394/2016 adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pyramax

International non-proprietary name: pyronaridine / artesunate

Procedure No. EMEA/H/W/002319/II/0002

Note

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

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List of abbreviations

ACPR	Adequate clinical and parasitological response
ACT	artemisinin-based combination therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AL	artemether/lumefantrine
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AS	Artesunate
ASAQ	Artesunate/amodiaquine
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-∞	area under the curve from time 0 to infinity
AUC0-last	area under the curve from time 0 to last measurable concentration
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	peak plasma or blood concentration
CV	coefficient of variation
DHA	Dihydroartemisinin
DHA-PQP	Dihydroartemisinin/piperaquine
ECG	electrocardiogram
EE	efficacy evaluable
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
MQ	mefloquine
MQ + AS	mefloquine + artesunate
P. falciparum	Plasmodium falciparum
P. vivax	Plasmodium vivax
PA	pyronaridine tetraphosphate/artesunate
PCR	polymerase chain reaction
PP	pyronaridine tetraphosphate
PSUR	Periodic Safety Update Report
PQ	primaquine
QTcB	QT using Bazett correction
QTcF	QT using Fridericia correction
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System Organ Class
t1/2	half-life
t1/2β	terminal half-life
tmax	time to peak plasma or blood concentration
TBM	“to-be-marketed”
ULN	upper limit of normal
ULRR	upper limit of the reference range
V2/F	volume of distribution in central compartment (pyronaridine population pharmacokinetics [popPK]) or volume of distribution (AS/DHA popPK)
V3/F	volume of distribution in peripheral compartment (pyronaridine popPK) or in central compartment (AS/DHA popPK)
V4/F	volume of distribution in peripheral compartment (AS/DHA popPK)
WANECAM	West African Network for Clinical Trials of Anti-malarial Drugs
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to section 10 of the CHMP "Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the community" (EMEA/CHMP/5579/04), Shin Poong Pharmaceutical Co., Ltd. submitted to the EMA on 12 March 2014 an application for a variation[1] to the CHMP Scientific Opinion.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The SOH applied for an extension of the indication to remove restrictions on repeated courses of treatment in any patient and use only in areas of low transmission with evidence of artesmisinin resistance. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4 and 4.8 of the SmPC. In addition, a minor editorial adjustment is proposed to SmPC section 5.1. The Package Leaflet was proposed to be updated in accordance. A revised RMP version 8 was provided as part of the application.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Not applicable.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

[1] Which corresponds, by analogy, to a Type II variation pursuant to Commission Regulation (EC) 1234/2008

1.2. Steps taken for the assessment of the product

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

Rapporteur: Joseph Emmerich Co-Rapporteur: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	12 March 2014
Start of procedure	28 March 2014
CHMP Rapporteur Assessment Report	21 May 2014
CHMP Co-Rapporteur Assessment Report	21 May 2014
PRAC Rapporteur Assessment Report	27 May 2014
Committees comments on PRAC Rapp Advice	2 June 2014
PRAC Rapporteur updated Assessment Report	N/A
PRAC outcome	12 June 2014
CHMP comments	16 June 2014
CHMP Rapporteur updated Assessment Report	19 June 2014
1st Request for supplementary information (RSI)	26 June 2014
SOH's responses submitted to the CHMP on	7 October 2014
CHMP Rapporteur response Assessment Report	2 December 2014
PRAC Rapporteur response Assessment Report	2 December 2014
Committees comments on PRAC Rapp Advice	N/A
PRAC Rapporteur updated response Assessment Report	N/A
PRAC outcome	4 December 2014
CHMP comments	8 December 2015
2nd Request for supplementary information (RSI)	18 December 2014
SOH's responses submitted to the CHMP on	19 February 2015
PRAC Rapporteur response Assessment Report	26 March 2015
CHMP Rapporteur response Assessment Report	26 March 2015
Committees comments on PRAC Rapp Advice	N/A
PRAC Rapporteur updated response Assessment Report	N/A
SAG experts meeting to address questions raised by the CHMP	30 March 2015
PRAC outcome	10 April 2015
CHMP comments	13 April 2015
3rd Request for supplementary information (RSI)	23 April 2015
SOH's responses submitted to the CHMP on	23 July 2015
CHMP Rapporteur response Assessment Report	1 September 2015
PRAC Rapporteur response Assessment Report	25 August 2015

Timetable	Actual dates
Committees comments on PRAC Rapp Advice	28 August 2015
PRAC Rapporteur updated response Assessment Report	2 September 2015
PRAC outcome	10 September 2015
CHMP comments	14 September 2015
4th Request for supplementary information (RSI)	24 September 2015
SOH's responses submitted to the CHMP on	19 October 2015
PRAC Rapporteur response Assessment Report	28 October 2015
CHMP Rapporteur response Assessment Report	30 October 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	6 November 2015
CHMP comments	11 November 2015
Rapporteur updated response Assessment Report	16 November 2015
CHMP Opinion	19 November 2015

2. Scientific discussion

2.1. Introduction

Pyramax (pyronaridine-artesunate: PA) is an antimalarial agent belonging to the artemisinin-based combination therapies (ACTs) class.

Medicinal product and pharmacotherapeutic 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.

Rationale/background for the proposed change

Malaria is a significant global health challenge affecting mainly young children and pregnant women, with approximately 500 million cases and up to 3 million deaths per year.

To counter the threat of resistance of *Plasmodium falciparum* to monotherapies and to improve treatment outcome, the WHO recommends in their guidelines that artemisinin-based combination therapies (ACTs) be used for the treatment of uncomplicated falciparum malaria. A number of ACTs are now available and include artesunate-amodiaquine (ASAQ), artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHA-PQP) which have shown to be well tolerated and efficacious in treating uncomplicated *P. falciparum* malaria in patients from endemic countries and are now often first or second line therapies in these countries.

Pyramax Tablets received positive Opinion under Article 58 by the Committee for Medicinal Products for Human Use (CHMP) of European Medicines Agency in February 2012 and are indicated in the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in adults and children weighing 20 kg or more, in areas of low transmission with evidence of artemisinin resistance, with Pyramax (PA) to be used only as a single treatment course in any given patient, especially in view of its hepatotoxic potential.

In most malaria endemic areas and especially those of medium to high endemicity, a person may be infected on multiple occasions during any one malaria season. This can occur in both children and adults. The need for re-dosing is dependent on the re-infection rate and varies according to geographic region and season. The imperative for ACTs to be allowed to be administered on more than one occasion is clear and a body of work has been undertaken with Pyramax since the Positive Opinion to address this.

A longitudinal study (SP-C-013-11) has been undertaken in three West African countries which allowed Pyramax to be tested over a number of malaria seasons in patients presenting with uncomplicated malaria. This longitudinal study involves the two new ACTs, Pyramax (PA) and DHA- piperaquine (DHA-PQ), compared to the local first line ACT therapies, being either ASAQ or AL depending on the site. The study examined safety and efficacy of these ACTs given for consecutive malaria episodes over a two year follow-up period. A sub-study analysis and clinical sub-study report is the basis of a submission to the European Medicinal Agency to amend the Summary of Product Characteristics (SmPC) regarding repeat administration of Pyramax for the treatment of recurrent malaria episodes. Moreover the SOH also provided a specific summary of potential mechanism associated with hepatic biochemistry parameter elevations in PA trials.

Proposed change of indication

4.1 Therapeutic indications

Pyramax tablets are indicated in the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in adults and children weighing 20 kg or more~~, in areas of low transmission with evidence of artemisinin resistance~~.

~~Pyramax is to be used only as a single treatment course in any given patient (see section 4.2 and 4.4.).~~

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

2.2. Non-clinical aspects

Potential mechanisms of hepatotoxicity of pyronaridine have been approached by the SOH in several studies.

2.2.1. Pharmacology

The SOH submitted two study reports:

1. *Study to explore the potential for pyronaridine to impair mitochondrial function (A Borgne-Sanchez)*

This study revealed that Pyronaridine induces mitochondrial alterations in isolated mouse liver mitochondria and more strongly in human cultured hepatocytes. Consequently, hepatotoxicity of

Pyronaridine which occurs in a small proportion of treated subjects during clinical trials could be attributed to mitochondrial toxicity.

2. *Cytotoxicity of pyronaridine in primary hepatocytes (Xiaoli Meng)*

This study concluded that Pyronaridine had a potent cytotoxic effect on primary hepatocytes (rat and human), and the cytotoxicity is dependent on the intracellular glutathione level or the glutathione redox cycle and may be caused by oxidative damage. Consequently, Quinone reductase, transporter, or glutathione reductase may play an important role in the detoxifying process.

2.2.2. Ecotoxicity / environmental risk assessment

An environmental risk assessment is not legally required for a request for Scientific Opinion under Article 58 of Regulation (EC) No 726/2004, and therefore has not been submitted with this this application.

2.2.3. Conclusion on the non-clinical aspects

Based on the non-clinical investigation as part of this application, knowledge has been gained on the mechanistic aspects of the toxicity. This seems a dose dependent mechanism which involves, as for paracetamol, the formation of a hepatotoxic reactive metabolite which could be detoxified by glutathion (GSH).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

2.3.2. Clinical pharmacology

No new data were provided.

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose response studies were performed.

2.4.2. Main study

WANECAM (SP-C-013-11) study:

A Phase IIIb/IV Comparative, Randomised, Multi-centre, Open Label, Parallel 3-arm Clinical Study to Assess the Safety and Efficacy of Repeated Administration of Pyronaridine-artesunate, Dihydroartemisinin-piperaquine or Artemether-lumefantrine or Artesunate-amodiaquine over a 2-year Period in Children and Adult Patients with Acute Uncomplicated*Plasmodium* sp. Malaria

Sub-study:

Sub-study analysis to assess the safety of repeat dosing of pyronaridine-artesunate for the treatment of recurrent malaria episodes (from ongoing WANECAM study SP-C-013-11).

Methods

An interim analysis of the longitudinal phase IIIb/IV study (**SP-C-013-11**) is submitted.

SP-C-013-11 (WANECAM) is an ongoing comparative, randomised, multi-centre, open label parallel 3-arm clinical study to assess the safety and efficacy of repeated administration of PA, or DHA-PQ versus AL or ASAQ over a 2-year period in children and adult patients with acute uncomplicated *Plasmodium sp.* malaria. PA is being compared to either AL or ASAQ depending on the site and first line therapy. In the sub-study which supports the repeat dosing, the efficacy population includes those patients who were at sites where PA and AL were administered. This allows for examination with comparable data from the phase III PA versus AL comparative pivotal studies.

Table 1 : Treatments per Study centre

Country	Study Centre	Test products	Comparator
Mali	Sotuba	PA; DHA-PQP	AL
Mali	Kolle	PA; DHA-PQP	AL
Mali	Bougoula-Hameau	PA; DHA-PQP	ASAQ or AL
Burkina Faso	Niangoloko-Banfora	PA; DHA-PQP	ASAQ
Burkina Faso	Bobo-Dioulasso	PA; DHA-PQP	AL
Guinea	Maferenya	PA; DHA-PQP	ASAQ

This study is being conducted in an area of **medium** transmission rate (2.5 to 2.8 infection /2 years per patient) and **moderate to high malaria endemicity population** in West Africa, where PA is administered to treat subsequent episodes of malaria, provided that the patient has not experienced transaminase rises more than 5 x upper limit of normal (ULN) or Hy's Law after the initial or previous treatment.

A sub-study interim analysis of SP-C-013-11 was planned for when sufficient patients had been re-dosed to demonstrate non-inferiority of PA repeated dosing to first dosing using a non-inferiority margin of 5% with a power of at least 80%. These data form the basis of the submission in support of a SmPC variation regarding PA repeated dosing for treatment of recurrent malaria episodes. The sub-study analysis assesses the safety of PA re-treatment, based on hepatotoxicity events rate as well as efficacy in this population. This coupled with a review of other safety parameters provide information with regard to the identified potential risk associated with repeat dosing.

Rationale / discussion of study design and the choice of control group

Review of the WANECAM study data by the independent DSMB concluded that there was no apparent difference in incidence or severity of liver function abnormalities from first to subsequent doses in the WANECAM study and that no difference in the AEs reported was noted between first and subsequent doses.

Given these initial findings, a decision was made to conduct a formal sub-study analysis on the sub-group of patients in the PA/comparator arm of the study, with a cut-off of 31 October 2013. This supports the filing of a variation of the label for PA tablets to allow for re-administration to patients with subsequent episodes of malaria. The suitability and acceptability of non-inferiority between treatment with PA for first and subsequent malaria episodes of events of ALT rises >5 x ULN or Hy's law with a non-inferiority margin of 5% and power of 80% was discussed with the CHMP Rapporteur and Co-Rapporteur on 12 April 2013.

The sub-study population comprises all patients treated with PA or AL only, in the period from the start of the study (October 2011) to the last enrolment on or by 31 October 2013 (with the last follow-up visit, for the purposes of this sub-study analysis, on 12 December 2013).

Patients who received PA at study centres where ASAQ was used as the comparator (instead of AL) were included in this sub-study.

Objectives

The overall primary objective of the WANECAM study is to compare the incidence of uncomplicated malaria episodes in children and adults treated with ACT over a follow-up period of 2 years. In this 3-arm non-inferiority study, PA and DHA-PQP are compared to either ASAQ or AL (depending on the study centre location). Pyronaridine tetraphosphate/artesunate and DHA-PQP are not formally compared.

The **primary** objective of the present sub-study analysis is to assess the safety of repeat administrations of PA in patients with recurrent episodes of malaria, in a sub-group of patients from the WANECAM study.

The exploratory objective of the present sub-study is to assess the efficacy of the first dose of PA compared with AL in order to allow the population treated in this WANECAM study to be compared to the African population treated in the phase III program.

Study participants

- **Main inclusion criteria :**

1. Age:

- For ASAQ, AL, and DHA-PQP: male or female patients ≥6 months of age

- For PA: male or female patients ≥15 years of age. After a DSMB review (first 20 PA patients re-treated at least once) reduced to age ≥2 years. After the second DSMB review (first 40 PA patients re-treated at least once) reduced to ≥6 months of age.

2. Body weight:

- For ASAQ, AL, and DHA-PQP: patients with a body weight ≥5 kg with no clinical evidence of severe malnutrition

- For PA: patients with a body weight ≥24 kg with no clinical evidence of severe malnutrition. After a DSMB review (first 20 PA patients re-treated at least once) patients with a body weight ≥15 kg with no clinical evidence of severe malnutrition. After the second DSMB review (first 40 PA patients re-treated at least once): patients with a body weight ≥5 kg with no clinical evidence of severe malnutrition.

3. Presence of acute uncomplicated *Plasmodium* sp. malaria by:

- Fever, as defined by axillary temperature ≥37.5°C or oral/rectal/tympanic temperature≥38°C, or history of fever in the previous 24 hours (not needed at re-inclusion) and,

- Positive microscopy of *Plasmodium* sp. with parasite density <200,000 parasites/µL

Main exclusion criteria

1. Patients with signs and symptoms of severe/complicated malaria requiring parenteral treatment according to the WHO criteria (2000).
2. Severe vomiting, defined as >3 times in the 24 hours prior to inclusion in the study or inability to tolerate oral treatment, or severe diarrhoea, defined as 3 or more watery stools per day.
3. Known history or evidence of clinically significant disorders such as cardiovascular (including arrhythmia, QTc interval _450 msec [a QT interval of _450 msec corrected for heart rate using either Bazett's formula {QTcB} or Fridericia's formula {QTcF} is acceptable]), respiratory (including active tuberculosis), history of jaundice, hepatic, renal, gastrointestinal, immunological (including active human immunodeficiency virus [HIV]-acquired immunodeficiency syndrome [AIDS]), neurological (including auditory), endocrine, infectious, malignancy, psychiatric (active depression, recent history of depression, generalised anxiety, psychosis, schizophrenia, or other major psychiatric disorders), history of convulsions, or any other abnormality (including recent head trauma).
4. Presence of significant anaemia, as defined by haemoglobin <7 g/dL.
5. Presence of febrile conditions caused by diseases other than malaria at the first inclusion and if oral treatment is not possible for the subsequent episode.
6. Known history of hypersensitivity, allergic or adverse reactions to pyronaridine, lumefantrine, or amodiaquine (for study centres where these were administered) piperaquine or artesunate or other artemisinins.
7. Use of any other anti-malarial agent, including traditional medicines, within 2 weeks prior to the start of the study
8. Female patients of child-bearing potential (≥12 years) are to be neither pregnant (as demonstrated by a negative pregnancy test) nor lactating, and not planning on becoming pregnant during the 42-day period after treatment.
9. Received an investigational drug within the previous 4 weeks.
10. Known or suspected chronic alcohol abuse, >3 units/day in men and >2 units/day in women.
11. Known active hepatitis A antibody, hepatitis B surface antigen, or hepatitis C antibody.
12. Known positive for HIV antibody.

13. Liver function tests (ALT levels) >2 x ULN

14. Known significant renal impairment, as indicated by serum creatinine of >1.5 x ULN.

Re-treatment Criteria

Patients have to fulfil all of the following criteria to be eligible for re-treatment during the 28-day follow-up period:

1. Outside active follow-up presence of acute uncomplicated *Plasmodium* sp. Malaria defined by:
    - Fever, as defined by axillary temperature ≥ 37.5°C or oral/rectal/tympanic temperature≥38°C, or history of fever or any other malaria symptom and,
    - Positive microscopy of *Plasmodium* sp. with parasite density <200,000 parasites/µL
2. During active follow-up, at or after the Day 28 scheduled visit, patients with symptomatic parasitaemia are to be re-treated with the ACT allocated at initial randomisation.

Temporary Non-re-treatment Criteria

Treatment administration is to be temporarily discontinued if a patient meets any of the following criteria at the time of re-treatment of a new malaria episode:

1. Patients with signs and symptoms of severe/complicated malaria requiring parenteral treatment according to the WHO (2000)
2. Severe vomiting, defined as >3 times in the 24 hours prior to inclusion in the study or inability to tolerate oral treatment, or severe diarrhoea defined as 3 or more watery stools per day
3. Liver function (ALT levels) >2 x ULN
4. Active acute hepatitis A, hepatitis B, or hepatitis C
5. Known significant renal impairment as indicated by serum creatinine of >1.5 x ULN
6. Positive microscopy of *Plasmodium* sp. with parasite density ≥200,000 parasites/µL
7. Ongoing SAE not related to the study drug
8. Parasite relapse before the Day 28 scheduled visit follow-up
9. Use of any other anti-malarial agent, other than the one used for malaria rescue treatment or severe malaria
10. Significant arrhythmia or prolonged QTc >450 msec during previous treatment or QTc >450 msec at the time of presentation for re-treatment
11. Pregnant or breastfeeding at the time of presentation for re-treatment

Any patient with a subsequent infection with malaria who fulfils the re-treatment criteria can be re-treated according to the protocol.

Removal of Patients from Therapy or Assessment

Treatment administration should be discontinued or the patient should be withdrawn from the study if any of the following criteria are met:

1. An SAE related to the study drug
2. Hypersensitivity, allergy to study drug
3. Sustained prolongation of QTc (>450 msec) related to treatment
4. Active chronic hepatitis B or hepatitis C
5. Known positive for HIV
6. Liver function (ALT levels) abnormality related to the study drug, isolated increase of ALT >5 x ULN or Hy's law (ALT >3 x ULN and total bilirubin >2 x ULN)
7. Travel outside the vicinity of the study centre for longer than 3 months
8. Any other medical condition in the opinion of the investigator that may jeopardise the patient's safety if she/he continues receiving the study drug. Such a condition is to be documented in details and the study monitor is to be notified immediately
9. Consent withdrawal

Study Sub-population for the Present Sub-study

For the current sub-study only patients treated with PA or AL who were enrolled into the WANECAM study on or by 31 October 2013 were included in the analysis.

Patients who received PA at study centres where ASAQ was used as the comparator (instead of AL) were included in this sub-study.

Treatments

Treatments Administered

The treatments administered per study centre are presented in Table 1. The study drug was taken orally and the number of tablets or granule sachets was dependent on the patient's weight.

Identity of Investigational Products (Sub-study Only)

Pyramax: pyronaridine tetraphosphate/artesunate (PA)

Depending on their body weight patients received a total of between 1 to a maximum of 4 tablets or 1 to 3 sachets per day administered at the same time of day (for 3 consecutive days). The dose in each tablet was 180:60 mg pyronaridine artesunate, and 60:20 mg for each granule sachet.

Oral Pyramax tablets and granules:

- 1 sachet with granules from 5 to <8 kg
- 2 sachets with granules from 8 to <15 kg
- 3 sachets with granules from 15 to <20 kg
- 1 tablet from 20 to <24 kg

- 2 tablets from 24 to <45 kg
- 3 tablets from 45 to <65 kg
- 4 tablets from ≥65 kg

Only the tablet formulation was to be used until the first DSMB review. The DSMB adjudicated when it was appropriate for granules to be used for children, initially 15 kg and above and on a further review to 5 kg and above.

The Pyramax tables and granules were supplied by Shin Poong.

Coartem-Dispersible® and Coartem®: artemether-lumefantrine (AL)

Administered twice daily for 3 days. The second dose was to be administered 8 hours (±1 hour) after the first dose. The four other doses were given twice daily (morning and evening). A minimum of 8 hours was to be observed between 2 doses.

Ideally the doses were to be administrated as follows after Dose 1: for Dose 2 (at Hour 8), the administration time window was not to be > ±1 hour. For the following doses at Hours 24, 36, 48, and 60 (twice daily), the time window was to be no > ±2 hours.

Depending on their body weight, patients received either Coartem-Dispersible or Coartem tablets (both formulations containing 20 mg artemether and 120 mg lumefantrine per tablet):

- 1 dispersible tablet from 5 to <15 kg
- 2 dispersible tablets from 15 to <25 kg
- 3 tablets from 25 to <35 kg
- 4 tablets for ≥35 kg

Further study drugs administered in the WANECAM study, but not to patients included in the population analysed for this sub-study report were DHA-PQP and ASAQ, as described in the WANECAM study protocol.

Method of Assigning Patients to Treatment Groups

At the first visit, all patients who fulfilled all the inclusion/exclusion criteria were given the lowest available number on the randomisation list. This number assigned them to one of the treatment arms. The investigator entered the randomisation number on the CRF.

The randomisation numbers were generated to ensure that treatment assignment was unbiased. To ensure efficient use of experimental drug supplies, independent randomization lists were produced by or under the responsibility of the sponsor using a validated system that automated the random assignment of treatment arms to randomisation numbers in the specified ratio. The randomisation scheme was reviewed by a Quality Assurance Group and locked by them after approval.

Selection of Doses in the Study

The dose levels administered in this study were dependent on the patients' weight and were in accordance with the product labels.

Outcomes/endpoints

The following endpoints were selected for the present sub-study report to enable an assessment of the impact of repeat administrations of PA, and do not represent all of the endpoints of the WANECAM study.

Safety (Primary)

- The occurrence of hepatotoxicity events, defined as alanine aminotransferase (ALT)>5 times the upper limit of normal (ULN) or Hy's law (ALT or aspartate aminotransferase [AST] >3 x ULN and total bilirubin >2 x ULN) at any post-dose time point (the time point being discrete and following each treatment i.e., after the first dose, after the second dose, after the third dose, and so forth)

- Monitoring of adverse events (AEs), vital signs, safety laboratory parameters, and electrocardiogram (ECG)

Efficacy (Exploratory)

- Day 28/Day 42 crude adequate clinical and parasitological response (ACPR), using the WHO definition

- Parasite clearance time (PCT), defined as the time from first dose within the current episode until continued disappearance of asexual *P. falciparum* parasites which remained at least a further 48 hours.

Sample size

The aim of the sub-study analysis is to demonstrate non-inferiority of PA repeated administrations to the first administration in terms of the primary safety endpoint with a non-inferiority margin of 5%. Simulation studies show that with 120, 150, and 190 re-dosed patients, the sub-study analysis was to have 80.8%, 85.9%, and 91.4% power to demonstrate the non-inferiority, respectively.

Randomisation

Blinding (masking)

This was an open label design study. The microscopists in charge of reading malaria smears were to be kept blinded until the malaria smear results were available. Smear readers were not to have access to the treatment record and were not to participate in the assessment and treatment of the participants. This was because the parasite outcome was very critical in determining the primary endpoint (malaria incidence) as well as the efficacy outcomes of the overall WANECAM study.

Statistical methods

Statistical and Analytical Plans

The following patient populations were defined for the sub-study analysis:

- The primary safety population was defined as all patients from the PA arm who received at least 1 dose of the study drug
- The secondary safety population was defined as all patients from the PA arm who received at least 2 dosing episodes of the study drug
- The overall safety population was defined as all patients from the PA/AL arm and PA patients from the AL/ASAQ arm who received at least 1 dose of the study drug
- The repeat dose safety population was defined as all patients from the PA/AL arm and PA patients from the AL/ASAQ arm who received at least 1 repeat dose of the study drug
- The repeat dose safety sub-population 1 (any repeat dose within 60 days) was defined as all patients from the PA/AL arm and PA patients from the AL/ASAQ arm who received at least 1 repeat dose of the study drug between any 2 treatment episodes within the given time frame
- The repeat dose safety sub-population 2 (any repeat dose within 90 days) was defined as all patients from the PA/AL arm and AL patients from the AL/ASAQ arm who received at least 1 repeat dose of the study drug between any 2 treatment episodes within the given time frame
- The repeat dose safety sub-population 3 (all repeat doses >90 days) was defined as all patients from the PA/AL arm and AL patients from the AL/ASAQ arm who received all repeat doses of the study drug >90 days after the preceding dose
- The primary randomised efficacy population was defined as all patients from the overall safety population excluding patients from the study centres that used ASAQ as comparator

Patient Disposition

Patient disposition was summarized with the number and percentage of patients who were randomized, treated, received at least 1, 2, 3, and so forth courses of the study drug, who discontinued the study prematurely, and who were still continuing in the study at the time of the data cut-off for the sub-study, by treatment arm. Further, the reasons for premature discontinuation from the study were summarized and a summary of the number and percentage of patients in each analysis population was provided. The time between each 2 courses of study drug was also summarized as continuous variables and categorically (0 to 30 days, 0 to 60 days, 0 to 90 days, 28 to 60 days, 61 to 90 days, and >90 days) and a summary of the number of patients randomized by country and study centre was provided.

Demographic Data and Baseline Characteristics

Demographic data and baseline characteristics were presented by treatment arm for each analysis population (PA and AL). Demographic data were also presented by study centre.

Data were summarized with the number of observations, mean, standard deviation (SD), minimum, median, quartiles, and maximum for continuous variables and with number and percentage of patients for categorical variables. For baseline *P. falciparum* parasite counts, the geometric mean was presented additionally.

Continuous variables were age, height, weight, and baseline *P. falciparum* total parasite count.

Categorical variables were gender, ethnicity, age category (<18 years, _18 years, for patients

<18 years this was further categorized as ≤2 years, >2 to 5 years, >5 years), body weight category (<20 kg, ≥20 kg). Age and weight at baseline of the first treatment episode were used for the subgroup analyses based on these variables. For age, the analysis <18 years versus ≥18 years was planned in the first place. If the sample size in the sub-categories of patients below 18 allowed a reasonable subgroup analysis, this may have been added.

Efficacy

Since the primary purpose of this sub-study was safety, only selected efficacy endpoints were analyzed in an exploratory way. Parasitaemia in the following sections refers to *P. falciparum* asexual parasites.

The following efficacy endpoints were presented by treatment episode (first, second, third, and so forth) and treatment arm:

- Day 28/Day 42 crude ACPR, using the WHO definition 2009
- PCT, defined as the time from first dose within the current episode until continued disappearance of asexual *P. falciparum* parasites which remained at least a further 48 hours.

WHO Definition of ACPR

The ACPR was defined as the absence of parasitaemia on Day 28 (or Day 42), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure.

Early Treatment Failure

- Danger signs or severe malaria on Days 1, 2, or 3 in the presence of parasitaemia
- Parasitaemia on Day 2 higher than on Day 0, irrespective of axillary temperature
- Parasitaemia on Day 3 with axillary temperature≥37.5°C
- Parasitaemia on Day 3≥25% of count on Day 0

Late Clinical Failure

- Danger signs or severe malaria in the presence of parasitaemia on any day between Day 4 and Day 28 (or Day 42) in patients who did not previously meet any of the criteria of early treatment failure
- Presence of parasitaemia on any day between Day 4 and Day 28 (or Day 42) with axillary temperature ≥37.5°C in patients who did not previously meet any of the criteria of early treatment failure

Late Parasitological Failure

- Presence of parasitaemia on any day between Day 4 and Day 28 (or Day 42) with axillary temperature <37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure

Descriptive statistics and exact 95% confidence intervals (CIs; calculated according to Pearson Clopper method) were presented for ACPR rates by treatment episode and treatment arm.

A Generalised Estimating Equation (GEE) model was used to estimate the treatment effect in cure rates over all treatment cycles between the PA arm and the AL arm. The GEE model used the cure as binary dependent variable, randomized treatment arm (PA, AL) as fixed effects, patient as random effect, and was estimated using the SAS procedure GENMOD with an identity link function and an exchangeable covariance structure. The GEE model analysis was performed separately for Day 28 and Day 42.

Patients who received rescue medication or concomitant medication with anti-malarial activity were considered a treatment failure from the time of rescue medication intake onwards in the crude analysis.

Parasite Clearance Time

The PCT was defined as the time (in hours) from the first dose of the study drug within the current episode until the time of first blood collection with disappearance of asexual parasites. Parasite clearance was defined as zero presence of *P. falciparum* asexual parasites which remained at least a further 48 hours.

The PCT was summarized with Kaplan-Meier estimates by treatment episode. Medians and quartiles were presented together with their 95% CI. Patients who did not have (confirmed) parasite clearance were censored at the time of their last available parasite count within the episode of interest.

Exposure

The number and percentage of patients who received 1, 2, 3, and so forth treatment episodes was summarized by treatment arm, together with the number of days between the first and the second, the second and the third etc. treatment episodes, as well as the average number of days between each 2 treatment episodes per patient. Days between treatment periods were calculated as start date of second episode minus start date of first episode plus 1.

The number and percentage of patients who received the study drug as tablets or pediatric formulation (sachets/granules for PA and dispersible tablets for AL) per treatment episode were presented overall and by body weight category.

Safety

The primary safety endpoint was defined as the occurrence of hepatotoxicity events (with event being defined as ALT >5 x ULN or Hy's law [ALT or AST >3 x ULN and total bilirubin >2 x ULN]) at any post-dose time point (a dose time point being discrete and following each treatment i.e., after the first, second, third or more dose).

The following statistical hypothesis was evaluated:

Let п2 denote the event rate of hepatotoxicity after re-dosing in the PA arm, and let п2 denote the event rate of hepatotoxicity after initial dosing in the PA arm. The hypothesis is:

H0: п2- п1≥ Δ versus the alternative HA: п2- п1< Δ

GEE model was used for the primary safety analysis. The GEE model had the primary safety endpoint as binary dependent variable, dosing (any repeated dosing versus first dosing) as the fixed effect, patient as the random effect. The SAS procedure GENMOD with an identity link function and an exchangeable covariance structure was used for estimation. A 95% one-sided upper confidence limit was computed from GEE model for the difference п2- п1. Re-dosing was intended to be judged not inferior to the initial dosing if the upper confidence limit was less than D, where D=5%, the predetermined non-inferiority margin.

The primary safety endpoint analysis was performed on the primary safety population. In the GEE model the "Dosing" variable had two categories, i.e.:

Initial dosing: all data of patients who received the first dosing

Repeated dosing: all data of patients who received two or more dosing

In addition, the above GEE model was applied on each patient's worst value per episode, i.e., each episode was treated as unit of analysis and the outcome variable was whether or not a patient had a hepatotoxicity event in each episode.

The analysis of the primary safety endpoint was also performed on the secondary safety population. In the GEE model analysis, the "dosing" variable had the following two categories:

Second dosing: all data of patients who received the second dosing

Third or more dosing: all data of patients who received three or more doses

The primary safety endpoint was further summarized descriptively by episode and treatment, by body weight subgroup and treatment and by the following time intervals between any 2 consecutive episodes: ≥30 days, ≥60 days, ≥90 days, 28 to 60 days, 61 to 90 days and >90 days.

Adverse Events

All AEs that were entered into the database were coded using the MedDRA Version 16.1 for summarization. They were attributed to the treatment episode when they occurred based on their start date. All AEs which started after the first dose of the first treatment episode, but before the first dose of the second treatment episode were counted for the first, etc.

The following AE summaries were generated by treatment arm and by treatment episode:

- An overview of the number and percentage of patients with:
  - Any AE
  - Any SAE
  - Any severe or life-threatening AE
  - Any AE considered to be related to study drug was defined as possible, probable, definite, or missing relationship, as assessed by the investigator. If the relationship to the study drug was missing, the worst case was assumed, i.e., such AEs were also considered to be related to the study drug
  - Any SAE considered to be related to the study drug
  - Any AE leading to death
  - Any AE leading to death considered to be related to study drug
- Number and percentage of patients with AEs by MedDRA primary System Organ Class

(SOC) and Preferred Term (PT) by treatment arm and episode

- Number and percentage of patients with study drug related AEs (defined as possible, probable, definite, or missing relationship to study drug) by MedDRA primary SOC and

PT by treatment arm and episode

- Number and percentage of patients with SAEs by MedDRA primary SOC and PT by treatment arm and episode
- Number and percentage of patients with AEs by MedDRA primary SOC, PT, and maximal severity, by treatment arm and episode
- Number and percentage of patients with hepatotoxicity-related AEs, based on the

Standard MedDRA Query (SMQ) narrow search “Drug-related hepatic disorders”

The above summaries were provided for each analysis population and were repeated by body weight categories (<20 kg, ≥20 kg) and age categories (<18 years, ≥18 years).

The AEs were further summarised by time interval between two consecutive episodes

(≤30 days, ≤60 days, ≤90 days, 28 to 60 days, 61 to 90 days, and >90 days).

Listings of all AEs as well as of all SAEs were provided. The treatment episode was indicated on these listings.

Clinical Laboratory Measurements

Clinical laboratory data (AST, ALT, total and conjugated bilirubin, ALP, serum creatinine, hemoglobin, platelet count, white blood count, neutrophils, lymphocytes, eosinophils) were summarized by

treatment episode and time point, including changes from Day 0 (pre-dose of each episode) and changes from the corresponding time point of the first episode, with the number of observations, mean, SD, median, quartiles, minimum, and maximum.

Incidence of liver enzyme abnormalities were summarised by time point and for the worst (highest) value per episode based on the criteria defined in the SAP. Shift tables of these categories at Day 0 of each treatment episode versus the worst post-baseline value were generated.

Changes in the Planned Analyses

There were three modifications of the original SAP for this sub-study:

- The first modification newly introduced an analysis of the primary safety endpoint, overall AE incidence and incidence of potential QTc prolongation by time between each

2 episodes, a summary of the primary safety endpoint and demographic data by study centre and an analysis of hepatotoxicity using each patient's worst case per dosing period.

These modifications were done after the dry-run review meeting on 20 October 2013.

- The second modification, dated 07 January 2014, clarified the handling of the use of rescue treatment within the efficacy analysis, the handling of quinine/artesunate treatment episodes and added the coding of concomitant medications.
- The third modification, dated 30 January 2014, included an additional efficacy analysis for the newly defined intent-to-treat efficacy population. Further, the pre-planned

PCR-corrected analysis of the ACPR was removed since this data had not been available at the time point of the database lock.

- The fourth modification, dated 10 February 2014, renamed the intent-to-treat efficacy population to the primary randomised efficacy population.

Results

Participant flow

Patient disposition is presented in Table 2.

Table 2 Patient Disposition and Exposure (overall safety population)

	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Total n (%)
Patients randomised	1015 (100.0)	671 (100.0)	1686 (100.0)
Patients treated (at least one dose)			
1 episode	1015 (100.0)	671 (100.0)	1686 (100.0)
2 episodes	316 (31.1)	238 (35.5)	554 (32.9)
3 episodes	84 (8.3)	81 (12.1)	165 (9.8)
4 episodes	28 (2.8)	20 (3.0)	48 (2.8)
5 episodes	4 (0.4)	4 (0.6)	8 (0.5)
6 episodes	1 (0.1)	1 (0.1)	2 (0.1)
7 episodes	1 (0.1)	0 (0.0)	1 (0.1)
8 episodes	1 (0.1)	0 (0.0)	1 (0.1)
9 episodes	1 (0.1)	0 (0.0)	1 (0.1)
Patients who completed study	0 (0.0)	0 (0.0)	0 (0.0)
Patients continuing in study at time point of sub-study analysis	992 (97.7)	657 (97.9)	1649 (97.8)
Withdrawn from study prematurely	23 (2.3)	14 (2.1)	37 (2.2)
During active treatment period	11 (1.1)	6 (0.9)	17 (1.0)
During post-treatment follow-up	12 (1.2)	7 (1.0)	19 (1.1)
Other time point	0 (0.0)	1 (0.1)	1 (0.1)
Reason for withdrawal			
Treatment failure	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	1 (0.1)	0 (0.0)	1 (0.1)
Death	1 (0.1)	1 (0.1)	2 (0.1)
Protocol violation	3 (0.3)	1 (0.1)	4 (0.2)
Lost to follow-up	4 (0.4)	1 (0.1)	5 (0.3)
Withdrawal of consent	9 (0.9)	7 (1.0)	16 (0.9)
Pregnancy	1 (0.1)	2 (0.3)	3 (0.2)
Study terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Other	4 (0.4)	2 (0.3)	6 (0.4)
Reason not yet databased	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on the number of randomised patients

In total, 1686 patients (100.0%) were eligible for the sub-study; 1015 patients were randomised to the PA arm and 671 patients to the AL arm at the data cut-off of 31 October 2013. The first patient was randomised in Sotuba, Mali, on 24 October 2011.

The number of PA patients in the study included both patients enrolled at study centres with AL as comparator as well as from study centres with ASAQ as comparator. At the time of data cut-off for the sub-study analysis, 1649 patients continued in the WANECAM study (992 patients in the PA arm and 657 in the AL arm).

In the PA arm, 11 patients (1.1%) were withdrawn during the active treatment period and 12 patients (1.2%) during the post-treatment follow-up The most frequently reported reason for a patient discontinuing from study participation was withdrawal of consent (9 patients [0.9%]). One patient in the PA arm was withdrawn due to an AE and 1 patient died.

Of the 671 patients in the AL arm, 14 patients (2.1%) were prematurely withdrawn: 3 patients (1.3%) with body weight <20 kg and 11 patients (2.5%) with body weight ≥20 kg. In the AL arm 6 patients (0.9%) were withdrawn during the active treatment period and 7 patients (1.0%) during the post-treatment follow-up. The most frequently reported reason for a patient discontinuing from study participation was withdrawal of consent (7 patients [1.0%]). No patients in the AL arm were withdrawn due to an AE and 1 patient died.

1015 patients with *P. falciparum* malaria have been dosed at least once with PA with 316 patients who have had courses of PA repeated at least once. In the under 20 kg patient population, 128 of 393

patients were dosed more than once over the analysis period, while in the 20 kg and over group, 188 of 622 patients were dosed more than once (cfr Table 3).

In this sub-study, all patients receiving PA are included in the safety analyses, but the efficacy analysis was repeated to include only patients randomised to PA at study centres using AL as comparator, as data from the ASAQ arm were not included in this sub-study analysis. Data from patients randomised to PA at study centres using ASAQ as comparator had to be excluded from the repeat analysis in order to make an informal comparison with first episode treatment in previous studies against AL.

Table 3: Patients treated by weight (< 20 kg or ≥20 kg) for first and consecutive episodes and time interval between episodes

	Pyronaridine/Artesunate		**Artemether/Lumefantrine**	
Episode 1	n=1015	100%	n=671	100%
< 20 kg	393	38.7%	233	34.7%
≥ 20 kg	622	61.3%	438	65.3%
Episode 2	n=316	100%	n=238	100%
< 20 kg	128	40.5%	84	35.3%
≥ 20 kg	188	59.5%	154	64.7%
Median time between Ep 1 and 2 (Days)	< 20 kg	≥ 20 kg	< 20 kg	≥ 20 kg
	49.0	78.0	43.5	78.0
Episode 3	n=84	100%	n=81	100%
< 20 kg	37	16.4%	20	24.7%
≥ 20 kg	47	83.6%	61	75.3%
Median time between Ep 2 and 3 (Days)	< 20 kg	≥ 20 kg	< 20 kg	≥ 20 kg
	43.0	70.0	44.0	65.0
Episode 4	n=28	100%	20	100%
< 20 kg	9	32.1%	2	10%
≥ 20 kg	19	67.9%	18	90%
Median time between Ep 3 and 4 (Days)	< 20 kg	≥ 20 kg	< 20 kg	≥ 20 kg
	41.0	57.0	35.0	71.0
Episode 5	n=4	100%	n=4	100%
< 20 kg	2	50%	0	0%
≥ 20 kg	2	50%	4	100%
Median time between Ep 4 and 5 (Days)	< 20 kg	≥ 20 kg	< 20 kg	≥ 20 kg
	33.5	146.0	N/A	34.5

The median time between treatment episodes 1 and 2, episodes 2 and 3, episodes 3 and 4, and episodes 4 and 5 were broadly similar across the treatment arms but differed by weight category. The median time between treatment episodes was longer for patients with body weight ≥20 kg than for patients with body weight <20 kg.

The proportion of patients re-dosed by time category between episode 1 and episode 2 is shown in Table 4.

Table 4 Patients Treated According to Time Between Episode 1 and Episode 2: <20 kg or ≥20 kg (Overall Safety Population)

	Pyronaridine artesunate		Artemether lumefantrine	
n (%)	<20 kg	≥20 kg	<20 kg	≥20 kg
28 to 60 days	83 (64.8)	68 (36.2)	55 (65.5)	66 (42.9)
61 to 90 days	25 (19.5)	39 (20.7)	13 (15.5)	16 (10.4)
>90 days	20 (15.6)	81 (43.1)	16 (19.0)	72 (46.8)
≤30 days	3 (2.3)	4 (2.1)	14 (16.7)	12 (7.8)
≤60 days	83 (64.8)	68 (36.2)	55 (65.5)	66 (42.9)
≤90 days	108 (84.4)	107 (56.9)	68 (81.0)	82 (53.2)

Baseline data

Demographic characteristics: presented in Table 5

Table 5 Demographic Characteristics (overall safety population)

Variable/ Statistic/Category	Pyronaridine artesunate (N=1015)	Artemether lumefantrine (N=671)	Total (N=1686)
Gender, n (%)			
Male	506 (49.9)	352 (52.5)	858 (50.9)
Female	509 (50.1)	319 (47.5)	828 (49.1)
Age (years)			
Available observations	1015	671	1686
Mean	10.1	11.7	10.7
Standard deviation	8.58	9.65	9.05
Minimum	0	0	0
Q1	5.0	5.0	5.0
Median	8.0	9.0	8.0
Q3	13.0	15.0	14.0
Maximum	62	69	69
Age category, n (%)			
<18 years	902 (88.9)	573 (85.4)	1475 (87.5)
<=6 months	3 (0.3)	2 (0.3)	5 (0.3)
>6 months - <1 year	6 (0.7)	3 (0.5)	9 (0.6)
1-2 years	82 (9.1)	32 (5.6)	114 (7.7)
3-5 years	233 (25.8)	145 (25.3)	378 (25.6)
6-17 years	578 (64.1)	391 (68.2)	969 (65.7)
>=18 years	113 (11.1)	98 (14.6)	211 (12.5)
Ethnicity group, n (%)			
Bamanan	67 (6.6)	64 (9.6)	131 (7.8)
Bozo	3 (0.3)	6 (0.9)	9 (0.5)
Dioula	7 (0.7)	5 (0.7)	12 (0.7)
Dogon	5 (0.5)	3 (0.4)	8 (0.5)
Goin	44 (4.3)	0 (0.0)	44 (2.6)
Guerze	4 (0.4)	0 (0.0)	4 (0.2)
Karaboro	4 (0.4)	0 (0.0)	4 (0.2)
Kissi	3 (0.3)	0 (0.0)	3 (0.2)
Malinke	116 (11.4)	112 (16.7)	228 (13.5)
Minianka	10 (1.0)	5 (0.7)	15 (0.9)
Mossi	114 (11.2)	81 (12.1)	195 (11.6)
Peulh	54 (5.3)	29 (4.3)	83 (4.9)
Sarakole	11 (1.1)	10 (1.5)	21 (1.2)
Senoufo	217 (21.4)	209 (31.2)	426 (25.3)
Sonrhai	5 (0.5)	2 (0.3)	7 (0.4)
Soussou	166 (16.4)	3 (0.4)	169 (10.0)
Other	184 (18.1)	141 (21.0)	325 (19.3)
Missing	1 (-)	1 (-)	2 (-)

Table 5 Demographic Characteristics (overall safety population) (continued)

Variable/ Statistic/Category	Pyronaridine artesunate (N=1015)	Artemether lumefantrine (N=671)	Total (N=1686)
Height (cm)			
Available observations	1015	671	1686
Mean	127.7	132.7	129.7
Standard deviation	27.11	27.39	27.32
Minimum	65.0	70.2	65.0
Q1	107.0	110.0	108.0
Median	126.5	131.0	128.4
Q3	150.0	157.0	153.5
Maximum	190.0	199.0	199.0
Body weight (kg)			
Available observations	1015	671	1686
Mean	28.7	31.8	29.9
Standard deviation	16.58	18.15	17.29
Minimum	6.7	7.8	6.7
Q1	16.3	16.8	16.5
Median	23.0	25.5	24.0
Q3	37.2	45.0	41.2
Maximum	84.2	100.6	100.6
Body weight category, n (%)			
<20 kg	393 (38.7)	233 (34.7)	626 (37.1)
>=20 kg	622 (61.3)	438 (65.3)	1060 (62.9)
Body mass index (kg/m^2)			
Available observations	1015	671	1686
Mean	16.05	16.44	16.20
Standard deviation	3.052	3.432	3.214
Minimum	10.5	8.0	8.0
Q1	14.15	14.15	14.15
Median	15.26	15.46	15.32
Q3	16.91	17.88	17.23
Maximum	35.6	38.3	38.3

Missing values were not included in the calculation of percentages.

The mean age and body mass index (BMI), percentage of patients in each age category (<18 years; ≤6 months; >6 months to <1 year; 1 to 2 years; 3 to 5 years; 6 to 17 years; ≥18 years), and distribution of males and females were similar between the treatment arms. Data from the repeat dose safety population were similar.

Baseline Disease Characteristics

The baseline *P. falciparum* parasite counts are presented in Table 6

Table 6 Baseline *Plasmodium falciparum* Parasite Counts (Overall safety population)

Variable/ Statistic/Category	Pyronaridine artesunate (N=1015)	Artemether lumefantrine (N=671)	Total (N=1686)
P. falciparum asexual forms at Day 0 of first episode (/uL)			
Available observations	1012	665	1677
Geometric mean *			
Mean	36162.3	40918.0	38048.1
Standard deviation	55203.4	48334.3	52623.6
Minimum	0	0	0
Q1	1650.0	4740.0	2720.0
Median	16400.0	24640.0	19360.0
Q3	51530.0	56160.0	52780.0
Maximum	1044200	279000	1044200
P. falciparum gametocytes at Day 0 of first episode (/uL)			
Available observations	996	648	1644
Geometric mean *			
Mean	1.0	1.2	1.1
Standard deviation	9.5	15.7	12.3
Minimum	0	0	0
Q1	0.0	0.0	0.0
Median	0.0	0.0	0.0
Q3	0.0	0.0	0.0
Maximum	216	320	320

* Geometric mean was only calculated if all counts were >0.

The mean and median *P. falciparum* asexual forms and gametocytes were lower in the PA arm than in the AL arm at baseline.

Numbers analysed

The number of each population is presented in Table 7

Table 7 Summary of Patient Populations

Population	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Total n (%)
Overall safety population	1015 (100.0)	671 (100.0)	1686 (100.0)
Primary safety population	1015 (100.0)	-	-
Secondary safety population	316 (31.1)	-	-
Repeat dose safety population	316 (31.1)	238 (35.5)	554 (32.9)
Repeat dose safety sub population 1 #	173 (17.0)	142 (21.2)	315 (18.7)
Repeat dose safety sub population 2 *	236 (23.3)	171 (25.5)	407 (24.1)
Repeat dose safety sub population 3 $	80 (7.9)	67 (10.0)	147 (8.7)
Primary randomised efficacy population	673 (66.3)	671 (100.0)	1344 (79.7)

Percentages are based on the number of randomised patients.
any repeat dosing ≤ 60 days after preceding dosing.
* any repeat dosing ≤ 90 days after preceding dosing (includes population 1).
$ all repeat dosings > 90 days after preceding dosing.

Outcomes and estimation

Parasitaemia

The Day 28 and Day 42 crude ACPR rate for episodes 1, 2, 3 and 4 is presented in Table 8 and 9 respectively. The rate during episodes 5, 6, 7, 8 and 9 is not displayed as <1% of patients had more than 4 episodes.

Table 8 Day 28 Crude Adequate Clinical and Parasitological Response Rate for Episodes 1, 2, 3 and 4 (Primary Randomised Efficacy Population)

Treatment episode	Statistic	Pyronaridine artesunate (N=673)	Artemether lumefantrine (N=671)
1	Available observations	648	645
	Number (%) of patients with ACPR	619 (95.5)	528 (81.9)
	95% confidence interval (Pearson Clopper)	93.6 - 97.0	78.7 - 84.8
	Number (%) of treatment failures	29 (4.5)	117 (18.1)
	Early treatment failure	2 (0.3)	1 (0.2)
	Late clinical failure	3 (0.5)	23 (3.6)
	Late parasitological failure	10 (1.5)	86 (13.3)
	Use of rescue medication	14 (2.2)	7 (1.1)
2	Available observations	208	228
	Number (%) of patients with ACPR	194 (93.3)	187 (82.0)
	95% cotionnfidence interval (Pearson Clopper)	89.0 - 96.3	76.4 - 86.8
	Number (%) of treatment failures	14 (6.7)	41 (18.0)
	Early treatment failure	0 (0.0)	0 (0.0)
	Late clinical failure	2 (1.0)	12 (5.3)
	Late parasitological failure	7 (3.4)	25 (11.0)
	Use of rescue medication	5 (2.4)	4 (1.8)
3	Available observations	61	75
	Number (%) of patients with ACPR	56 (91.8)	64 (85.3)
	95% confidence interval (Pearson Clopper)	81.9 - 97.3	75.3 - 92.4
	Number (%) of treatment failures	5 (8.2)	11 (14.7)
	Early treatment failure	0 (0.0)	0 (0.0)
	Late clinical failure	1 (1.6)	2 (2.7)
	Late parasitological failure	4 (6.6)	8 (10.7)
	Use of rescue medication	0 (0.0)	1 (1.3)
4	Available observations	22	18
	Number (%) of patients with ACPR	21 (95.5)	15 (83.3)
	95% confidence interval (Pearson Clopper)	77.2 - 99.9	58.6 - 96.4
	Number (%) of treatment failures	1 (4.5)	3 (16.7)
	Early treatment failure	0 (0.0)	0 (0.0)
	Late clinical failure	0 (0.0)	1 (5.6)
	Late parasitological failure	1 (4.5)	2 (11.1)
	Use of rescue medication	0 (0.0)	0 (0.0)

ACPR: adequate clinical and parasitological response rate
Patients with no or missing *P. falciparum* asexual forms at Day 0 were not taken into account for cure calculation.

Table 9 Day 42 Crude Adequate Clinical and Parasitological Response Rate for Episodes 1, 2, 3 and 4 (Primary Randomised Efficacy Population

Treatment episode	Statistic	Pyronaridine artesunate (N=673)	Artemether lumefantrine (N=671)
1	Available observations	624	628
	Number (%) of patients with ACPR	518 (83.0)	425 (67.7)
	95% confidence interval (Pearson Clopper)	79.8 - 85.9	63.9 - 71.3
	Number (%) of treatment failures	106 (17.0)	203 (32.3)
	Early treatment failure	2 (0.3)	1 (0.2)
	Late clinical failure	22 (3.5)	39 (6.2)
	Late parasitological failure	67 (10.7)	155 (24.7)
	Use of rescue medication	15 (2.4)	8 (1.3)
2	Available observations	193	218
	Number (%) of patients with ACPR	137 (71.0)	139 (63.8)
	95% confidence interval (Pearson Clopper)	64.0 - 77.3	57.0 - 70.1
	Number (%) of treatment failures	56 (29.0)	79 (36.2)
	Early treatment failure	0 (0.0)	0 (0.0)
	Late clinical failure	14 (7.3)	17 (7.8)
	Late parasitological failure	37 (19.2)	56 (25.7)
	Use of rescue medication	5 (2.6)	6 (2.8)
3	Available observations	56	73
	Number (%) of patients with ACPR	37 (66.1)	49 (67.1)
	95% confidence interval (Pearson Clopper)	52.2 - 78.2	55.1 - 77.7
	Number (%) of treatment failures	19 (33.9)	24 (32.9)
	Early treatment failure	0 (0.0)	0 (0.0)
	Late clinical failure	2 (3.6)	6 (8.2)
	Late parasitological failure	17 (30.4)	17 (23.3)
	Use of rescue medication	0 (0.0)	1 (1.4)
4	Available observations	21	17
	Number (%) of patients with ACPR	17 (81.0)	12 (70.6)
	95% confidence interval (Pearson Clopper)	58.1 - 94.6	44.0 - 89.7
	Number (%) of treatment failures	4 (19.0)	5 (29.4)
	Early treatment failure	0 (0.0)	0 (0.0)
	Late clinical failure	1 (4.8)	1 (5.9)
	Late parasitological failure	3 (14.3)	4 (23.5)
	Use of rescue medication	0 (0.0)	0 (0.0)

ACPR: adequate clinical and parasitological response rate
Patients with no or missing *P. falciparum* asexual forms at Day 0 were not taken into account for cure calculation.

In the sub-group analysis of PA repeated dosing for subsequent malaria episodes in relation to that seen with AL, the outcomes to include 3 repeat cycles of dosing are presented in Table 10.

Table 10 Day 28 and 42 crude ACPR rate by episode for PA and AL based on weight range

	Pyronaridine / artesunate (n=673)		**Artemeter / lumefantrine (n=671)**	
Total patient numbers per body weight category	Body weight <20 kg n=213	Body weight >=20 kg n=460	Body weight <20 kg n=233	Body weight >=20 kg n=438
DAY 28 crude ACPR				
No. crude ACPR patients/ No. observations (%) at Day 28 EPISODE 1	188/202 (93.1)	431/446 (96.6)	158/228 (69.3)	370/427 (88.7)

No. crude ACPR patients/ No. observations (%) at Day 28 EPISODE 2	64/74 (86.5)	130/134 (97.0)	51/82 (62.2)	136/146 (93.2)
No. crude ACPR patients/ No. observations (%) at Day 28 EPISODE 3	18/22 (81.8)	38/39 (97.4)	12/18 (66.7)	52/57 (91.2)
No. crude ACPR patients/ No. observations (%) at Day 28 EPISODE 4	6/6 (100)	15/16 (93.8)	1/2 (50)	14/16 (87.5)
DAY 42 crude ACPR				
No. crude ACPR patients/ No. observations (%) at Day 42 EPISODE 1	135/195 69.2)	383/429 (89.3)	120/226 (53.1)	305/402 (75.9)
No. crude ACPR patients/ No. observations (%) at Day 42 EPISODE 2	34/66 (51.5)	103/127 (81.1)	37/78 (47.4)	102/140 (72.9)
No. crude ACPR patients/ No. observations (%) at Day 42 EPISODE 3	5/17 (29.4)	32/39 (82.1)	8/18 (44.4)	41/55 (74.5)
No. crude ACPR patients/ No. observations (%) at Day 42 EPISODE 4	3/5 (60,0)	14/16 (87.5)	1/2 (50.0)	11/15 (73.3)

The GEE estimates of crude ACPR are presented in Table 11

Table 11 Generalised Estimating Equation Estimates of Crude Adequate Clinical and Parasitological Response (Primary Randomised Efficacy Population)

		Pyronaridine artesunate (N=673)	Artemether lumefantrine (N=671)	Difference estimate for PA mins AL
Crude ACPR (%)				
Day 28	ACPR estimate	94.8	82.2	12.6
	95% confidence interval	(93.3, 96.2)	(79.6, 84.7)	(9.7, 15.6)
Day 42	ACPR estimate	80.5	67.6	12.9
	95% confidence interval	(77.8, 83.3)	(64.4, 70.8)	(8.7, 17.2)

ACPR: adequate clinical and parasitological response rate; AL: artemether-lumefantrine; PA: pyronaridine tetraphosphate/artesunate
Results estimated from the generalised estimating equation model with treatment group as fixed effect and patient as random effect.
Patients with no or missing *P. falciparum* asexual forms at Day 0 were not taken into account for cure calculation.

The patients randomized to PA at study centres using ASAQ as comparator were excluded from the repeat efficacy analysis (primary randomized efficacy population) so that an informal comparison with first episode treatment in previous studies against AL could be made. Therefore for the efficacy comparison between PA and AL the numbers of patients in each treatment arm were similar. The number of treatment failures was less in the PA arm than in the AL arm.

The difference estimate in episode 1 for PA minus AL in crude ACPR was 12.6 (94.8 in the PA arm and 82.2 in the AL arm) on Day 28 and 12.9 (80.5 in the PA arm and 67.6 in the AL arm) on Day 42. These differences are statistically significant at 5% with 95%CI being (9.7%; 15.6%) and (8.7%; 17.2%), respectively.

Overall, the ACPR on Day 28/42 in PA arm is comparable to the comparator.

Parasite Clearance Time

The Kaplan-Meier estimates are presented for episodes 1, 2, 3, and 4 in Table 12. The estimates during episodes 5, 6, 7, 8, and 9 are not displayed as <1% of patients had more than 4 episodes.

Table 12 Parasite clearance time Kaplan-Meier estimates of time

Parasite Clearance Time (hours)	**PA**	**AL**
EPISODE 1 Median PCT (95% CI)	24.8 (23.3 – 23.7)	34.5 (34.2 – 35.2)
EPISODE 2 Median PCT (95% CI)	24.1 (23.9 – 24.5)	24.2 (23.9 – 24,6)
EPISODE 3 Median PCT (95% CI)	23.9 (23.3 – 24.4)	24.4 (23.9 – 25.0)
EPISODE 4 Median PCT (95% CI)	24.1 (23.5 – 24.4)	24.1 (23.3 – 34.4)

Parasite clearance time remained consistent across repeated dosing for PA. Confidence intervals were tight around the median.

With the exception of a long PCT for the first episode, PCT for AL was in line with PA.

2.4.3. Discussion on clinical efficacy

Design and conduct of the clinical study

A longitudinal clinical study (SP-C-013-11) is being conducted in an area of medium transmission rate (3.29 malaria episodes per person over 2 years) in West Africa, where Pyramax is administered to treat subsequent episodes of *P. falciparum* malaria in patients of a minimum of 5 kg. This is a three-arm study comparing 4 ACTs. Sub-analyses were conducted to support the repeat dose variation for Pyramax tablets as well as a separate analysis in support of the line extension for the paediatric formulation with granules for oral suspension (procedure X-08).

Retreatment with Pyramax only takes place when an individual patient presents with a subsequent episode of malaria. This is influenced by a combination of malaria seasonality (whether malaria is still prevalent in the area) and, importantly, the treatment prophylaxis afforded by the antimalarial.

At the time of the analysis of the 1015 patients treated with Pyramax and presented in this variation, there were 316 patients treated for 2 or more episodes and 83 patients treated with Pyramax on 3 or more occasions; with 81 patients treated with at least 3 times with AL.

The study design, the choice of comparator arm and the method of analysis are acceptable for the demonstration of efficacy in this context.

Efficacy data and additional analyses

The efficacy analyses have been presented for the total trial population and by body weight category for specific parameters. The data presented is for patients 20 kg and greater who received the tablet formulation; while the other group represents patients receiving granules.

The estimate of crude ACPR was higher in the PA arm than in the AL arm on Day 28 (94.8% [95%CI: 93.3-96.2] vs 82.2% [95%CI: 79.6 – 84.7]) and Day 42 (80.5% [95%CI: 77.8-84.7] vs 67.6% [95%CI: 64.4 – 70.8]).

The median PCT was lower in the PA group than in the AL group during the first treatment episode and similar during the later treatment episodes. The clearance rate was complete by 72 hours in both treatment arms.

The Day 28 results indicate that the efficacy does not decrease with subsequent treatments. The Day 42 results show a less clear picture; however this is hampered by small sample size and 95%CIs overlap. There is a concern on the efficacy demonstration for episodes ≥ 3 because the number of patients is strongly reduced since episode 3 (only 39 patients>20 kg in PA arm versus 57 in AL arm). Further data with more patients are expected to confirm the efficacy for third episode and subsequent episodes.

2.4.4. Conclusions on the clinical efficacy

A full study report will contain all data from the longitudinal study SP-C-013-11 and should be reported by the end of 2016. The SOH commits to provide the full analyses in the study report to EMA on completion of the study.

2.5. Clinical safety

Introduction

The SOH intended to amend the Summary of Product Characteristics (SmPC) regarding repeat administration of PA for the treatment of recurrent malaria episodes based on the present sub-study analysis and a clinical sub-study report. Main new safety data came from this clinical sub-study analysis. Moreover regarding the specific safety concern of hepatotoxicity, a summary of potential mechanisms have also been submitted with this variation.

Study SP-C13-11

This sub-study is part of the WANECAM study which is an ongoing comparative, randomised, multi-centre, open label, parallel 3-arm study to assess the safety and efficacy of repeated ACT therapy over a follow-up period of 2 years in children and adults with uncomplicated *Plasmodium* sp. malaria at enrolment. At each study centre, eligible patients are randomised into 3 treatments arms: DHA-PQP, PA, or first line ACT treatment with either AL or ASAQ.

The primary objective of the present sub-study analysis is to assess the safety of repeat administrations of PA in patients with recurrent episodes of malaria, in a sub-group of patients from the WANECAM study. For the current sub-study only patients treated with PA or AL who were enrolled into the WANECAM study on or by 31 October 2013 were included in the analysis. Patients who received PA at study centres where ASAQ was used as the comparator were included in this sub-study.

The safety primary endpoints were:

- The occurrence of hepatotoxicity events, defined as alanine aminotransferase (ALT)>5 times the upper limit of normal (ULN) or Hy's law (ALT or aspartate aminotransferase [AST] >3 x ULN and total bilirubin >2 x ULN) at any post-dose time point (the time point being discrete and following each treatment i.e., after the first dose, after the second dose, after the third dose, and so forth)

The following statistical hypothesis was evaluated:
Let π_2 denote the event rate of hepatotoxicity after re-dosing in the PA arm, and let π_2 denote the event rate of hepatotoxicity after initial dosing in the PA arm. The hypothesis is:
H0: $\pi_2 - \pi_1 \geq \Delta$ versus the alternative HA: $\pi_2 - \pi_1 < \Delta$

- Monitoring of adverse events (AEs), vital signs, safety laboratory parameters, and electrocardiogram (ECG)

Patient exposure

In the PA arm, 31.1% of the patients were re-treated for a second episode; 8.3% for a third episode; 2.8% for a fourth episode; 0.4% for a fifth episode; and 0.1% for a sixth, seventh, eight, and ninth episode. The aforementioned is based on the data used for the sub-study analysis, as patients are still continuing in the WANECAM study and they are subject to more treatment episodes.

Table 13 : Patient Disposition and Exposure (Overall Safety Population)

	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Total n (%)
Patients randomised	**1015 (100.0)**	**671 (100.0)**	**1686 (100.0)**
Patients treated (at least one dose)			
1 episode	1015 (100.0)	671 (100.0)	1686 (100.0)
2 episodes	316 (31.1)	238 (35.5)	554 (32.9)
3 episodes	84 (8.3)	81 (12.1)	165 (9.8)
4 episodes	28 (2.8)	20 (3.0)	48 (2.8)
5 episodes	4 (0.4)	4 (0.6)	8 (0.5)
6 episodes	1 (0.1)	1 (0.1)	2 (0.1)
7 episodes	1 (0.1)	0 (0.0)	1 (0.1)
8 episodes	1 (0.1)	0 (0.0)	1 (0.1)
9 episodes	1 (0.1)	0 (0.0)	1 (0.1)
Patients who completed study	0 (0.0)	0 (0.0)	0 (0.0)
Patients continuing in study at time point of sub-study analysis	992 (97.7)	657 (97.9)	1649 (97.8)
Withdrawn from study prematurely	23 (2.3)	14 (2.1)	37 (2.2)
During active treatment period	11 (1.1)	6 (0.9)	17 (1.0)
During post-treatment follow-up	12 (1.2)	7 (1.0)	19 (1.1)
Other time point	0 (0.0)	1 (0.1)	1 (0.1)
Reason for withdrawal			
Treatment failure	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	1 (0.1)	0 (0.0)	1 (0.1)
Death	1 (0.1)	1 (0.1)	2 (0.1)
Protocol violation	3 (0.3)	1 (0.1)	4 (0.2)
Lost to follow-up	4 (0.4)	1 (0.1)	5 (0.3)
Withdrawal of consent	9 (0.9)	7 (1.0)	16 (0.9)
Pregnancy	1 (0.1)	2 (0.3)	3 (0.2)
Study terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Other	4 (0.4)	2 (0.3)	6 (0.4)

Of the 1015 patients in the PA arm, 23 patients (2.3%) were prematurely withdrawn: 8 patients (2.0%) with body weight <20 kg and 15 patients (2.4%) with body weight ≥20 kg.

In the PA arm, 11 patients (1.1%) were withdrawn during the active treatment period and 12 patients (1.2%) during the post-treatment follow-up The most frequently reported reason for a patient discontinuing from study participation was withdrawal of consent (9 patients [0.9%]). One patient in the PA arm was withdrawn due to an AE and 1 patient died.

Only one patient withdrew due to an adverse event and this was a case of mild vomiting in the PA treatment group. There were a number of patients who were not re-treated with PA because they met the non-redosing criteria defined in the protocol and these are outlined in Appendix 5 of the SOH as these criteria were a rise in ALT/AST > 5 x ULN or Hy's law; however, in at least 2 cases patients who met the non-redosing criteria were re-dosed in violation of the protocol.

The number of patients in each time between treatment episodes category (28 to 60 days; 61 to 90 days; >90 days; ≤30 days; ≤60 days; ≤90 days) varied between the treatment arms. The minimum time between treatment episodes in the PA arm was 28 days (between episode 2 and episode 3) and the maximum time between treatment episodes was 452 days (between episode 1 and episode 2). Caution is needed in interpretation of the mean time between episodes due to the seasonality of malaria at the study centres and therefore, median time between episodes is more informative.

The numbers of patients and median times between dosing by weight category <20 kg and ≥20 kg is shown in the following table; as there were so few patients re-dosed more than 4 times, only data up to episode 5 are shown.

Table 14: Patients Treated by Weight: <20 kg or ≥20 kg

	Pyronaridine / Artesunate		**Artemether / Lumefantrine**	
Episode 1 (overall safety population)	n=1015	100%	n=671	100%
<20 kg	393	38.7%	233	34.7%
≥20 kg	622	61.3%	438	65.3%
Episode 2 (repeat dose safety population)	n=316	100%	n=238	100%
<20 kg	128	40.5%	84	35.3%
≥20 kg	188	59.5%	154	64.7%
Median time between episodes 1 and 2 (days)	**<20 kg**	**≥20 kg**	**<20 kg**	**≥20 kg**
	49.0	78.0	43.5	78.0
Episode 3	n=84	100%	n=81	100%
<20 kg	37	44.0%	20	24.7%
≥20 kg	47	55.9%	61	75.3%
Median time between episodes 2 and 3 (days)	**<20 kg**	**≥20 kg**	**<20 kg**	**≥20 kg**
	43.0	70.0	44.0	65.0
Episode 4	n=28	100%	20	100%
<20 kg	9	32.1%	2	10%
≥20 kg	19	67.9%	18	90%
Median time between episodes 3 and 4 (days)	**<20 kg**	**≥20 kg**	**<20 kg**	**≥20 kg**
	41.0	57.0	34.0	71.5
Episode 5	n=4	100%	n=4	100%
<20 kg	2	50%	0	0%
≥20 kg	2	50%	4	100%
Median time between episodes 4 and 5 (days)	**<20 kg**	**≥20 kg**	**<20 kg**	**≥20 kg**
	33.5	146.0	N/A	34.5

Table 15 : Patients Treated According to Time Between Episode 1 and Episode 2: <20 kg or ≥20 kg (Overall Safety Population)

	Pyronaridine artesunate		Artemether lumefantrine	
n (%)	**<20 kg**	**≥20 kg**	**<20 kg**	**≥20 kg**
28 to 60 days	83 (64.8)	68 (36.2)	55 (65.5)	66 (42.9)
61 to 90 days	25 (19.5)	39 (20.7)	13 (15.5)	16 (10.4)
>90 days	20 (15.6)	81 (43.1)	16 (19.0)	72 (46.8)
total	128 (100.0)	188 (100.0)	84 (100.0)	154 (100.0)

It is noted that among the 316 PA-redosed patients, there were 188 patients weighing > 20 kg. Among these, only 68 patients weighing > 20kg have been retreated with PA with a delay of re-administration between 28-60 days.

Pyronaridine-artesunate over Time

The median time between treatment episodes was longer for patients with body weight ≥20 kg than for patients with body weight <20 kg (see table 14).

With subsequent episodes the number of patients <20 kg who were re-treated >90 days from the previous episodes reduced to zero; however, the overall number of patients in each subsequent episodes was relatively small.

Pyronaridine-artesunate Compared to Artemether-lumefantrine

The median time between treatment episodes 1 and 2, episodes 2 and 3, episodes 3 and 4, and episodes 4 and 5 were broadly similar across the treatment arms but differed by weight category (see table 14).

The median time between treatment episodes was similar between the treatment arms.

The need for re-administration was greater in the <20 kg weight category, with repeat doses administered in 65% of patients in the PA arm and AL arm after episode 1 within 28 to 60 days in the <20 kg category, compared to 36% for patients in the PA arm and 43% for patients in the AL arm in the ≥20 kg category.

Demographic characteristics

Demographic (i.e. gender, age) between the two arms and characteristics regarding the medicinal product exposure (i.e. median time between retreatment episodes notably depending weight categorisation) are similar.

Table 16 : Demographic and Baseline Characteristics – SP-C-013-11 Sub-study Population

Variable / Statistic / Category	PA (N=1015)	AL (N=671)
Gender, n (%)		
Male	506 (49.9)	352 (52.5)
Female	509 (50.1)	319 (47.5)
Age (years)		
Available observations	1015	671
Mean	10.1	11.7
Standard deviation	8.58	9.65
Minimum	0	0
Q1	5	5
Median	8	9
Q3	13	15
Maximum	62	69
Age category, n (%)		
< 18 years	902 (88.9)	573 (85.4)
≤ 6 months	3 (0.3)	2 (0.3)
> 6 months - < 1 year	6 (0.7)	3 (0.5)
1-2 years	82 (9.1)	32 (5.6)
3-5 years	233 (25.8)	145 (25.3)
6-17 years	578 (64.1)	391 (68.2)
≥ 18 years	113 (11.1)	98 (14.6)

Patients received PA tablets (each containing 180 mg pyronaridine/60 mg artesunate) or sachets (each containing 60 mg pyronaridine/20 mg artesunate) according to weight shown below:

Body weight	**Number of tablets**	**Regimen**
20 - < 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

Body weight	**Number of 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

The number of patients who received tablets or granules by weight category is shown in the following table.

Table 17 : Patients taking Tablets or Granules in sub-study SP-C-013-11

Episode 1				
< 20 kg		**≥ 20 kg**		**Total**
393		622		1015
Granules	**Tablets**	**Granules**	**Tablets**	
376 (95.7%	17 (4.3%)	30 (4.8%)	592 (95.2%)	
Episode 2+				
< 20 kg		**≥ 20 kg**		**Total**
128		188		316
Granules	**Tablets**	**Granules**	**Tablets**	
118 (92.2%)	10 (7.8%)	5 (2.7%)	183 (97.3%)	

Adverse events / serious adverse event / deaths / other significant events

Adverse events from the SP-C-013-11 sub-study are summarised below for episodes 1 and subsequent episodes. Overall, the proportions of adverse events were similar between the two treatment groups.

Table 18 : Overview of Treatment-Emergent Adverse Events

Treatment episode	Number (%) of patients with	PA (N=1015) n (%)	AL (N=671) n (%)
1	Number of patients dosed	1015 (100.0)	671 (100.0)
	Any adverse event	445 (43.8)	318 (47.4)
	Any drug-related adverse event *	206 (20.3)	144 (21.5)
	Any serious adverse event	11 (1.1)	5 (0.7)
	Any serious drug-related adverse event *	4 (0.4)	1 (0.1)
	Any severe or life-threatening adverse event	15 (1.5)	7 (1.0)
	Any adverse event leading to death	1 (0.1)	1 (0.1)
2+	Number of patients dosed	316 (100.0)	238 (100.0)
	Any adverse event	125 (39.6)	102 (42.9)
	Any drug-related adverse event *	56 (17.7)	46 (19.3)
	Any serious adverse event	2 (0.6)	0 (0.0)
	Any serious drug-related adverse event *	0 (0.0)	0 (0.0)
	Any severe or life-threatening adverse event	3 (0.9)	0 (0.0)
	Any adverse event leading to death	0 (0.0)	0 (0.0)

* Drug-related = possible, probable, definite or missing relationship to study drug.

In the repeat course safety populations, the incidence of adverse events and serious adverse events was similar or less frequent on repeat dosing compared with episode 1. The overall incidence appeared to be lowest in repeat dosing >90 days from the previous episode however, this was the smallest group with only 25% of patients being re-dosed after 90 days and some of these patients may have been treated in different seasons.

Table 19: Overview of PA adverse events, by episode (Repeat dose safety populations)

	Repeat	Subpop1	Subpop2	Subpop3
	All	<60 days	<90 days	> 90 days
	n (%)	n (%)	n (%)	n (%)
Treatment episode 1				
Number of patients dosed	316 (100.0)	173 (100.0)	236 (100.0)	80 (100.0)
Any adverse event	147 (46.5)	84 (48.6)	115 (48.7)	32 (40.0)
Any drug-related adverse event	63 (19.9)	36 (20.8)	50 (21.2)	13 (16.3)
Any serious adverse event	2 (0.6)	0 (0.0)	0 (0.0)	2 (2.5)
Any serious drug-related adverse event	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.3)
Any severe or life-threatening adverse event	3 (0.9)	1 (0.6)	1 (0.4)	2 (2.5)
Any adverse event leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment episode 2+				
Number of patients dosed	316 (100.0)	173 (100.0)	236 (100.0)	80 (100.0)
Any adverse event	125 (39.6)	82 (47.4)	105 (44.5)	20 (25.0)
Any drug-related adverse event	56 (17.7)	34 (19.7)	45 (19.1)	11 (13.8)
Any serious adverse event	2 (0.6)	0 (0.0)	1 (0.4)	1 (1.3)
Any serious drug-related adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any severe or life-threatening adverse event	3 (0.9)	0 (0.0)	1 (0.4)	2 (2.5)
Any adverse event leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

In the repeated dose safety populations (n=316), it is reassuring to observe that serious AEs are very rare (n=3) and no serious drug-related AE have been reported in the subpopulation 1 (delay of PA re-administration between 28-60 days). Subpopulation 1 represents the relevant categorisation for which cumulative effects of PA might be seen.

Deaths

There were two unrelated deaths in the SP-C-013-11 sub-study; in the PA arm multi-organ failure following a road traffic accident and in the AL arm HIV infection.

General data on adverse events

In the SP-C-013-11 sub-study the numbers of patients treated in episodes 1 to 3 were large enough to draw conclusions from the incidence of adverse events and comparison between treatment arms.

The adverse event profile for episode 1 was broadly in line with that seen in the Phase II/III programme although investigator reported AEs of QTc prolongation was reported more frequently in this sub-study. It is likely that this is due to a higher reporting in patients <20 kg who represented a greater proportion of the denominator in this sub-study than in the Phase II/III programme. An analysis of centrally read ECGs is provided in this Section.

The proportions of adverse events while remaining similar between treatment groups reduced with each episode of treatment

Related adverse events in ≥1% patients in any treatment group are shown in the following table. Again the pattern is similar between the treatment groups and between episodes although the smaller

number of patients treated in episode 3 meant that hyper creatinaemia was proportionally high in relations to previous episodes.

Table 20: Incidence of Treatment-Related Adverse Events Reported by at least 1% of Patients in any Treatment Arm by Primary System Organ Class and Preferred Term

	PA	AL
Primary system organ class		
Preferred term	**n (%)**	**n (%)**
Treatment episode 1		
Patients dosed	**1015 (100.0)**	**671 (100.0)**
At least one adverse event	**206 (20.3)**	**144 (21.5)**
Blood and lymphatic system disorders	56 (5.5)	48 (7.2)
Neutropenia	26 (2.6)	17 (2.5)
Anaemia	16 (1.6)	14 (2.1)
Monocytosis	11 (1.1)	11 (1.6)
Gastrointestinal disorders	49 (4.8)	12 (1.8)
Vomiting	30 (3.0)	9 (1.3)
Abdominal pain	15 (1.5)	1 (0.1)
Infections and infestations	14 (1.4)	13 (1.9)
Bronchitis	8 (0.8)	11 (1.6)
Investigations	93 (9.2)	73 (10.9)
Electrocardiogram QT prolonged	52 (5.1)	61 (9.1)
Alanine aminotransferase increased	27 (2.7)	6 (0.9)
Aspartate aminotransferase increased	26 (2.6)	10 (1.5)
Metabolism and nutrition disorders	8 (0.8)	12 (1.8)
Hypercreatininaemia	8 (0.8)	12 (1.8)
Treatment episode 2		
Patients dosed	**316 (100.0)**	**238 (100.0)**
At least one adverse event	**48 (15.2)**	**37 (15.5)**
Blood and lymphatic system disorders	9 (2.8)	17 (7.1)
Thrombocytopenia	4 (1.3)	0 (0.0)
Neutropenia	3 (0.9)	9 (3.8)
Monocytosis	2 (0.6)	4 (1.7)
Gastrointestinal disorders	7 (2.2)	3 (1.3)
Vomiting	4 (1.3)	3 (1.3)
Investigations	30 (9.5)	19 (8.0)
Electrocardiogram QT prolonged	20 (6.3)	14 (5.9)
Aspartate aminotransferase increased	8 (2.5)	1 (0.4)
Alanine aminotransferase increased	4 (1.3)	2 (0.8)
Metabolism and nutrition disorders	2 (0.6)	3 (1.3)

	PA	AL
Primary system organ class		
Preferred term	**n (%)**	**n (%)**
Hypercreatininaemia	2 (0.6)	3 (1.3)
Treatment episode 3		
Patients dosed	**84 (100.0)**	**81 (100.0)**
At least one adverse event	**11 (13.1)**	**13 (16.0)**
Blood and lymphatic system disorders	2 (2.4)	2 (2.5)
Anaemia	1 (1.2)	0 (0.0)
Neutropenia	1 (1.2)	1 (1.2)
Basophilia	0 (0.0)	1 (1.2)
Cardiac disorders	0 (0.0)	1 (1.2)
Bradycardia	0 (0.0)	1 (1.2)
Infections and infestations	1 (1.2)	5 (6.2)
Bronchitis	1 (1.2)	1 (1.2)
Rhinitis	1 (1.2)	3 (3.7)
Oral herpes	0 (0.0)	1 (1.2)
Investigations	5 (6.0)	3 (3.7)
Electrocardiogram QT prolonged	4 (4.8)	3 (3.7)
Blood creatinine increased	1 (1.2)	0 (0.0)
Metabolism and nutrition disorders	4 (4.8)	2 (2.5)
Hypercreatininaemia	4 (4.8)	2 (2.5)
Skin and subcutaneous tissue disorders	1 (1.2)	1 (1.2)
Dermatitis allergic	1 (1.2)	0 (0.0)
Prurigo	0 (0.0)	1 (1.2)

Adverse events of specific interest (Laboratory findings)

Hepatic disorders

In the sub-study of the longitudinal study SP-C-013-11 the main objective was to analyse the safety of repeated dosing with PA with particular reference to the potential for hepatotoxicity. Therefore, there was a collection of adverse events of special interest related to this hepatotoxicity as shown in the following table.

Table 21: Incidence of Hepatotoxicity-related Adverse Events by Standard MedDRA Query

	PA	AL
SMQ level 2 SMQ level 3 SMQ level 4 - Prefered term	n (%)	n (%)
Treatment Episode 1 - Patients dosed	**1015 (100.0)**	**671 (100.0)**

Drug related hepatic disorders - comprehensive search	38 (3.7)	18 (2.7)
Cholestasis and jaundice of hepatic origin	2 (0.2)	3 (0.4)
- Drug-induced liver injury	1 (0.1)	1 (0.1)
- Hyperbilirubinaemia	2 (0.2)	2 (0.3)
Drug related hepatic disorders - severe events only	1 (0.1)	1 (0.1)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	1 (0.1)	1 (0.1)
- Drug-induced liver injury	1 (0.1)	1 (0.1)
Liver related investigations, signs and symptoms	38 (3.7)	17 (2.5)
- Alanine aminotransferase increased	28 (2.8)	7 (1.0)
- Aspartate aminotransferase increased	29 (2.9)	10 (1.5)
- Blood bilirubin increased	0 (0.0)	2 (0.3)
- Hyperbilirubinaemia	2 (0.2)	2 (0.3)
- Transaminases increased	5 (0.5)	1 (0.1)
Treatment Episode 2 - Patients dosed	**316 (100.0)**	**238 (100.0)**
Drug related hepatic disorders - comprehensive search	11 (3.5)	6 (2.5)
Cholestasis and jaundice of hepatic origin	0 (0.0)	2 (0.8)
- Hyperbilirubinaemia	0 (0.0)	2 (0.8)
Liver related investigations, signs and symptoms	11 (3.5)	6 (2.5)
- Alanine aminotransferase increased	5 (1.6)	2 (0.8)
- Aspartate aminotransferase increased	9 (2.8)	1 (0.4)
- Bilirubin conjugated increased	0 (0.0)	1 (0.4)
- Hyperbilirubinaemia	0 (0.0)	2 (0.8)
Treatment Episode 3 - Patients dosed	**84 (100.0)**	**81 (100.0)**
Drug related hepatic disorders - comprehensive search	1 (1.2)	0 (0.0)
Liver related investigations, signs and symptoms	1 (1.2)	0 (0.0)
- Aspartate aminotransferase increased	1 (1.2)	0 (0.0)

No hepatotoxicity-related AEs were reported for later episodes.

These events were more common in the PA-treated patients than in the AL-treated ones but the frequency of these events appeared to reduce with further dosing albeit in smaller numbers of treated patients.

The SOH particularly refers to the primary analysis of hepatotoxicity events (defined as rises in ALT > 5 ULN or ALT/AST >3 x ULN and total bilirubin >2 x ULN in the absence of a raised alkaline phosphatase [Hy's law]) based on first versus subsequent exposures.

Because the protocol's non re-dosing criteria prohibited re-dosing of patients with PA if they experienced one of these hepatotoxicity events, the statistical power of the study was set to measure the hepatotoxicity rate in the 1st treatment episode versus re-treatment with a non-inferiority margin of 5%. Non-inferiority was claimed when the upper limit of the 95% confidence interval was <5%. This was performed on the primary safety analysis population which was all PA patients who received at least one dose of the drug.

Table 22 : Analysis of Primary Safety Endpoint. Results from Generalised Estimating Equation Model (Primary Safety Population)

Event rate of primary safety endpoint		(%)
1	**Analysis based on all post-dose time points**	
	Estimate for initial dosing	0.5
	Estimate for repeat dosing	0.2
	Difference (repeat versus initial dosing)	
	Estimate	-0.3
	One-sided 95% CI upper limit	0
2	**Analysis based on post-dose worst case per episode**	
	Estimate for initial dosing	1.3
	Estimate for repeat dosing	0.5
	Difference (repeat versus initial dosing)	
	Estimate	-0.8
	One-sided 95% CI upper limit	0

The SOH also provided shift table for ALT in the PA arm for worst post-dose value for episode 1 and episodes 2+:

Table 23: Shift Table of ALT Categories from Pre-dose to the Worst Post-dose value, by Treatment Episode and Treatment (Overall Safety Population)

Number (%) of patients

	Total	<1.5 x ULN	>1.5-<=3 x ULN	>3-<=5 x ULN	>5-<=10 x ULN	>10 x ULN
Treatment Episode 1						
Total	995 100.0)	991 (99.6)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
<1.5 x ULN	926 (93.1)	924 (92.9)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
>1.5-<=3 x ULN	46 (4.6)	45 (4.5)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
>3-<=5 x ULN	10 (1.0)	9 (0.9)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
>5-<=10 x ULN	10 (1.0)	10 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>10 x ULN	3 (0.3)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment Episode 2						
Total	304 (100.0)	299 (98.4)	4 (1.3)	1 (0.3)	0 (0.0)	0 (0.0)
<1.5 x ULN	289 (95.1)	286 (94.1)	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)
>1.5-<=3 x ULN	12 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
>3-<=5 x ULN	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
>5-<=10 x ULN	2 (0.7)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
>10 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Among the overall safety population, it is shown that ALT rise >1.5xULN after the 1st PA adminsitration was observed for 69/995 patients (6.9%) with the following categorisation of transaminase rise:
- 46/995 of patients (4.6%) with ALT rise between 1.5-3xULN
- 10/995 of patient (1%) with ALT rise between 3-5xULN
- 10/995 of patients (1%) with ALT rise between 5-10xULN
- 3/995 of patients (0.3%) with ALT rise > 10xULN.
Frequency and seriousness of observed AST rise are comparable with the results of previous clinical trials submitted in the frame of the scientific opinion.

The ALT rise > 1.5xULN after PA re-adminsitrations was observed for 15/304 patients (4.9%) with the following categorisation of transaminase rise:
- 12/304 of patients (3.9%) with ALT rise between 1.5-3xULN
- 1/304 of patient (0.3%) with ALT rise between 3-5xULN
- 2/304 of patients (0.7%) with ALT rise between 5-10xULN
- no patient with ALT rise > 10xULN.
Frequency and seriousness of observed AST rise are comparable after the 1st and after the 2nd PA adminsitration. For other analyses of safety, several populations were defined including only those patients who were treated for more than one episode. Although these populations also included patients who received AL, this section refers only to patients receiving PA.

These safety populations were defined as:

- **Repeat dose**: all PA patients who received at least 1 repeat dose of the study drug
- **Repeat dose sub-population 1**: all PA patients who received at least 1 repeat dose of the study drug between any 2 treatment episodes within 60 days
- **Repeat dose sub-population 2**: all PA patients who received at least 1 repeat dose of the study drug between any 2 treatment episodes within 90 days
- **Repeat dose sub-population 3**: all PA patients who received all doses of the study >90 days after the preceding dose

Hepatotoxicity events as defined above were also summarised for the repeat dose safety populations and these are shown for episodes 1 to 3 in the table. It is observed that for patients who were treated more than once, fewer events occurred on repeat dosing and there was no relationship between hepatotoxicity events and short and longer periods between dose administrations. There were no events for episodes 4 and more.

Table 24: Raw incidence of PA hepatotoxicity events at any post dosing time point (Repeat dose populations)

	Repeat	Subpop1	Subpop2	Subpop3
	All	<60 days	<90 days	> 90 days
Treatment episode 1	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients dosed	316	173	236	80
Total number of post Day 0 liver function tests	917 (100.0)	506 (100)	689 (100)	228 (100)
Overall number of hepatotoxicity events (rate)	3 (0.3)	0 (0.0)	0 (0.0)	3 (1.3)
Patients with any post Day 0 liver function test	314 (100.0)	173 (100)	235 (100)	79 (100)
Patients with hepatotoxicity post Day 0	3 (1.0)	0 (0.0)	0 (0.0)	3 (3.8)
Treatment episode 2	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients dosed	316	173	236	80
Total number of post Day 0 liver function tests	877 (100.0)	472 (100)	646 (100)	231 (100)
Overall number of hepatotoxicity events (rate)	2 (0.2)	1 (0.2)	1 (0.2)	1 (0.4)
Patients with any post Day 0 liver function test	309 (100.0)	167 (100)	230 (100)	79 (100)
Patients with hepatotoxicity post Day 0	2 (0.6)	1 (0.6)	1 (0.4)	1 (1.3)
Treatment episode 3	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients dosed	84	66	78	6
Total number of post Day 0 liver function tests	229 (100.0)	181 (100)	211(100)	18(100)
Overall number of hepatotoxicity events (rate)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with any post Day 0 liver function test	81 (100.0)	65 (100)	75 (100)	6 (100)
Patients with hepatotoxicity post Day 0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

"Hepatotoxicity events" have been defined in the study report as ALT>5xULN or Hy's law (ALT or AST >3xULN and total bilirubin >2xULN) at any post-dose time point.

Changes in ALT Values relative to normal range

The following table shows the PA repeat dose populations for ALT changes relative to normal range by Day 0 of the episode and highest post dose value in the first and subsequent episodes. It is observed that ALT changes are not increased on repeat dosing and are not influenced by the time between dosing, particularly for significant rises >3 and > 5 x ULN.

Table 25 : Incidence of ALT values relative to the normal range, by treatment episode (Repeat dose populations)

		Repeat	Subpop1	Subpop2	Subpop3
		All	<60 days	<90 days	> 90 days
Treatment episode 1		n (%)	n (%)	n (%)	n (%)
Day 0	ALT ≤1.5 x ULN	316 / 316 (100.0)	173 / 173 (100.0)	236 / 236 (100.0)	80 / 80 (100.0)
	ALT >1.5 x ULN and ≤3 x ULN	0 / 316 (0.0)	0 / 173 (0.0)	0 / 236 (0.0)	0 / 80 (0.0)
	ALT >3 x ULN and ≤5 x ULN	0 / 316 (0.0)	0 / 173 (0.0)	0 / 236 (0.0)	0 / 80 (0.0)
	ALT >5 x ULN and ≤10 x ULN	0 / 316 (0.0)	0 / 173 (0.0)	0 / 236 (0.0)	0 / 80 (0.0)
	ALT >10 x ULN	0 / 316 (0.0)	0 / 173 (0.0)	0 / 236 (0.0)	0 / 80 (0.0)
Highest value post Day 0	ALT ≤1.5 x ULN	298 / 314 (94.9)	168 / 173 (97.1)	226 / 235 (96.2)	72 / 79 (91.1)
	ALT >1.5 x ULN and ≤3 x ULN	10 / 314 (3.2)	5 / 173 (2.9)	8 / 235 (3.4)	2 / 79 (2.5)
	ALT >3 x ULN and ≤5 x ULN	3 / 314 (1.0)	0 / 173 (0.0)	1 / 235 (0.4)	2 / 79 (2.5)
	ALT >5 x ULN and ≤10 x ULN	2 / 314 (0.6)	0 / 173 (0.0)	0 / 235 (0.0)	2 / 79 (2.5)
	ALT >10 x ULN	1 / 314 (0.3)	0 / 173 (0.0)	0 / 235 (0.0)	1 / 79 (1.3)
Treatment episode 2+					
Day 0	ALT ≤1.5 x ULN	302 / 308 (98.1)	164 / 168 (97.6)	225 / 230 (97.8)	77 / 78 (98.7)
	ALT >1.5 x ULN and ≤3 x ULN	5 / 308 (1.6)	4 / 168 (2.4)	4 / 230 (1.7)	1 / 78 (1.3)
	ALT >3 x ULN and ≤5 x ULN	1 / 308 (0.3)	0 / 168 (0.0)	1 / 230 (0.4)	0 / 78 (0.0)
	ALT >5 x ULN and ≤10 x ULN	0 / 308 (0.0)	0 / 168 (0.0)	0 / 230 (0.0)	0 / 78 (0.0)
	ALT >10 x ULN	0 / 308 (0.0)	0 / 168 (0.0)	0 / 230 (0.0)	0 / 78 (0.0)
Highest value post Day 0	ALT ≤1.5 x ULN	294 / 309 (95.1)	156 / 167 (93.4)	218 / 230 (94.8)	76 / 79 (96.2)
	ALT >1.5 x ULN and ≤3 x ULN	12 / 309 (3.9)	9 / 167 (5.4)	10 / 230 (4.3)	2 / 79 (2.5)
	ALT >3 x ULN and ≤5 x ULN	1 / 309 (0.3)	1 / 167 (0.6)	1 / 230 (0.4)	0 / 79 (0.0)
	ALT >5 x ULN and ≤10 x ULN	2 / 309 (0.6)	1 / 167 (0.6)	1 / 230 (0.4)	1 / 79 (1.3)
	ALT >10 x ULN	0 / 309 (0.0)	0 / 167 (0.0)	0 / 230 (0.0)	0 / 79 (0.0)

Hepatotoxicity-related adverse events based on MedDRA terms are shown in the following table for the PA repeat dose safety and sub-populations. There were no events for episodes 4 and more. In it can be observed that there is no increased risk of these events on repeat dosing independent of the time between doses.

Table 26: Incidence of PA hepatotoxicity related adverse events by standard MedDRA query (Repeat dose populations)

	Repeat	Subpop1	Subpop2	Subpop3
	All	<60 days	<90 days	> 90 days
Treatment episode 1	n (%)	n (%)	n (%)	n (%)
Patients dosed	**316 (100.0)**	**173 (100.0)**	**236 (100.0)**	**80 (100.0)**
Drug related hepatic disorders - comprehensive search	14 (4.4)	5 (2.9)	8 (3.4)	6 (7.5%)
Cholestasis and jaundice of hepatic origin	1 (0.3)			1 (1.3)
Drug-induced liver injury	1 (0.3)			1 (1.3)
Hyperbilirubinaemia	1 (0.3)			1 (1.3)
Drug related hepatic disorders - severe events only	1 (0.3)			1 (1.3)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	1 (0.3)			1 (1.3)
Drug-induced liver injury	1 (0.3)			1 (1.3)
Liver related investigations, signs and symptoms	14 (4.4)	5 (2.9)	8 (3.4)	6 (7.5%)
Alanine aminotransferase increased	11 (3.5)	3 (1.7)	5 (2.1)	6 (7.5%)
Aspartate aminotransferase increased	11 (3.5)	4 (2.3)	6 (2.5)	5 (6.3)
Hyperbilirubinaemia	1 (0.3)			1 (1.3)
Transaminases increased	2 (0.6)	1 (0.6)	2 (0.8)	
Treatment episode 2	n (%)	n (%)	n (%)	n (%)
Patients dosed	**316 (100.0)**	**173 (100.0)**	**236 (100.0)**	**80 (100.0)**
Drug related hepatic disorders - comprehensive search	11 (3.5)	6 (3.5)	6 (2.5)	5 (6.3)
Cholestasis and jaundice of hepatic origin	0 (0.0)			
Hyperbilirubinaemia	0 (0.0)			
Liver related investigations, signs and symptoms	11 (3.5)	6 (3.5)	6 (2.5)	5 (6.3)
Alanine aminotransferase increased	5 (1.6)	3 (1.7)	3 (1.3)	2 (2.5)

	Repeat	Subpop1	Subpop2	Subpop3
	All	**<60 days**	**<90 days**	**> 90 days**
Aspartate aminotransferase increased	9 (2.8)	5 (2.9)	5 (2.1)	4 (5.0)
Bilirubin conjugated increased	0 (0.0)			
Hyperbilirubinaemia	0 (0.0)			
Treatment episode 3	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients dosed	**84 (100.0)**	**66 (100.0)**	**78 (100.0)**	**6 (100.0)**
Drug related hepatic disorders - comprehensive search	1 (1.2)	1 (1.5)	1 (1.3)	
Liver related investigations, signs and symptoms	1 (1.2)	1 (1.5)	1 (1.3)	
Aspartate aminotransferase increased	1 (1.2)	1 (1.5)	1 (1.3)	

Table 27: Incidence of Hepatotoxicity-related Adverse Events by Standard MedDRA Query by Body Weight Category (Overall Safety Population)

	Body weight <20 kg		Body weight ≥20 kg	
SMQ level 2				
SMQ level 3	Pyronaridine	Artemether	Pyronaridine	Artemether
SMQ level 4	artesunate	lumefantrine	artesunate	lumefantrine
Preferred term	n (%)	n (%)	n (%)	n (%)
Treatment Episode 1				
Patients dosed	393 (100.0)	233 (100.0)	622 (100.0)	438 (100.0)
Drug related hepatic disorders - comprehensive search (SMQ)	14 (3.6)	11 (4.7)	24 (3.9)	7 (1.6)
Cholestasis and jaundice of hepatic origin (SMQ)	1 (0.3)	0 (0.0)	1 (0.2)	3 (0.7)
Drug-induced liver injury	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Hyperbilirubinaemia	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.5)
Drug related hepatic disorders - severe events only (SMQ)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Drug-induced liver injury	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Liver related investigations, signs and symptoms (SMQ)	14 (3.6)	11 (4.7)	4 (3.9)	6 (1.4)
Alanine aminotransferase increased	9 (2.3)	5 (2.1)	19 (3.1)	2 (0.5)
Aspartate aminotransferase increased	11 (2.8)	9 (3.9)	18 (2.9)	1 (0.2)
Blood bilirubin increased	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Hyperbilirubinaemia	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.5)
Transaminases increased	4 (1.0)	0 (0.0)	1 (0.2)	1 (0.2)
Treatment Episode 2				
Patients dosed	128 (100.0)	84 (100.0)	188 (100.0)	154 (100.0)
Drug related hepatic disorders - comprehensive search (SMQ)	6 (4.7)	5 (6.0)	5 (2.7)	1 (0.6)
Cholestasis and jaundice of hepatic origin (SMQ)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)
Hyperbilirubinaemia	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)
Liver related investigations, signs and symptoms (SMQ)	6 (4.7)	5 (6.0)	5 (2.7)	1 (0.6)
Alanine aminotransferase increased	2 (1.6)	1 (1.2)	3 (1.6)	1 (0.6)
Aspartate aminotransferase increased	5 (3.9)	1 (1.2)	4 (2.1)	0 (0.0)
Bilirubin conjugated increased	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Hyperbilirubinaemia	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)

No hepatotoxicity-related AEs were reported during episodes 4, 5, 6, 7, 8, or 9 and only 1 such an event was reported during episode 3: increased AST in the PA arm. No hepatotoxicity-related AEs were reported during episodes 3, 4, 5, 6, 7, 8, or 9 with AL. During episode 1, hepatotoxicity-related AEs were reported for 38 patients (3.7%) in the PA arm and 18 patients (2.7%) in the AL arm. The most frequently reported PTs were increased AST (2.9% in the PA arm and 1.5% in the AL arm) and increased ALT (2.8% in the PA arm and 1.0% in the AL arm). Other events reported were drug-induced liver injury (PA and AL), hyperbilirubinaemia (PA and AL), increased blood bilirubin (AL), and increased transaminases (PA and AL).

During episode 2, hepatotoxicity-related AEs were reported for 11 patients (3.5%) in the PA arm and 6 patients (2.5%) in the AL arm. The most frequently reported PTs were again increased AST (2.8% in the PA arm and 0.4% in the AL arm) and increased ALT (1.6% in the PA arm and 0.8% in the AL arm).

Overall, drug-related hepatic disorders were similar across the weight ranges and treatment arms except for the ≥20 kg category in the AL arm. Results for episode 1 were similar with a smaller group of patients

and there was no evidence of a higher incidence for the smaller children between the treatment arms and between first and second episodes. In the PA arm, the incidence of these events was similar between the 20 kg and ≥20 kg categories.

The primary safety endpoint for this sub-study was defined as the occurrence of hepatotoxicity events (with event being defined as ALT >5 x ULN or Hy's law [ALT or AST >3 x ULN and total bilirubin >2 x ULN]) at any post-dose time point.

The event rate of the primary safety endpoint is presented in Table below.

Table 28: Analysis of Primary Safety Endpoint: Results from Generalised Estimating Equation Model (Primary Safety Population)

Event rate of primary safety endpoint	(%)
(1) Analysis based on all post-dose time points	
Estimate for initial dosing	0.5
Estimate for repeat dosing	0.2
Difference (repeat versus initial dosing)	
Estimate	-0.3
One-sided 95% CI upper limit #	0.0
(2) Analysis based on post-dose worst case per episode	
Estimate for initial dosing	1.3
Estimate for repeat dosing	0.5
Difference (repeat versus initial dosing)	
Estimate	-0.8
One-sided 95% CI upper limit #	0.0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; ULN: upper limit of normal Hepatotoxicity was defined as ALT >5 x ULN or Hy's law (ALT or AST >3 x ULN and total bilirubin >2 x ULN) at any post-dosing time point.
Non-inferiority was claimed when the upper limit of the 95% confidence interval was <5%. Results estimated from the generalised estimating equation model with dosing (repeat versus first dosing) as fixed effect and patient as random effect.

Hepatotoxicity events, based on raw values (actual measurements), after Day 0 were reported for the following number of patients:

- Episode 1: 13 patients (1.3%) in the PA arm and 3 patients (0.5%) in the AL arm

- Episode 2: 2 patients (0.6%) in the PA arm and no patients in the AL arm

No hepatotoxicity events were reported for any patients during episodes 3, 4, 5, 6, 7, 8 or 9.

The 2 events during episode 2 in the PA arm were reported 28 to 60 days and >90 days after the first episode, respectively. Based on all post-dose time points, the estimated hepatotoxicity event rate was 0.5% and 0.2% for initial and repeat dosing, respectively. The estimated difference in the event rate between repeat and initial dosing was -0.3% with a 95% CI upper limit of 0.0. Based on the post-dose worst case per episode, the estimated hepatotoxicity event rate for initial administration was 1.3% and 0.5% for repeat administrations. The estimated difference in the event rate of repeat versus initial administration was -0.8% with a 95% CI upper limit of 0.0.

As the 95% CIs from the above analyses fall below the pre-defined non-inferiority margin of 5% with more than 90% power, the non-inferiority conclusion can be established in terms of the rate of hepatotoxicity events reported during repeated PA administrations compared to that of a single administration.

Scatter plots of peak bilirubin versus peak ALT ≥ Day 3, peak bilirubin versus peak AST ≥ Day 3, peak bilirubin versus peak ALT≥ Day 7, and peak bilirubin versus peak AST ≥ Day 7 are presented by treatment episode (Figure 1-4 below). Overall, the scatter plots were similar between the treatment arms.

Figure 1: Scatter Plot of Peak Bilirubin versus Peak ALT ≥ Day 3, by Treatment Episode (Overall Safety Population)

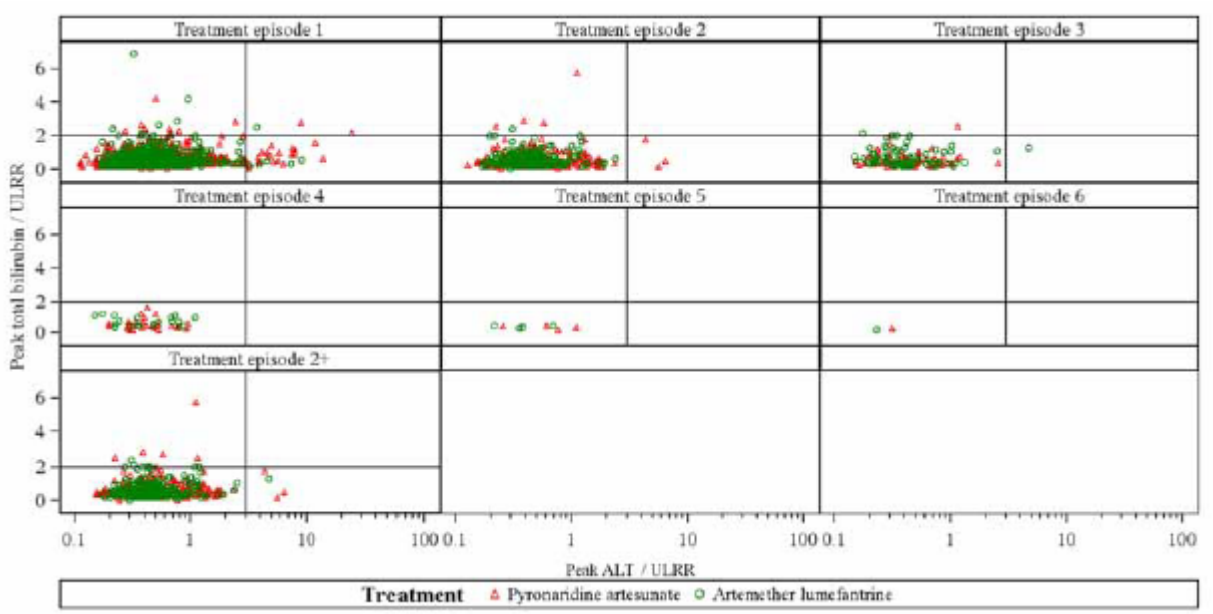


Figure 2: Scatter Plot of Peak Bilirubin versus Peak AST ≥Day 3, by Treatment Episode (Overall Safety Population)

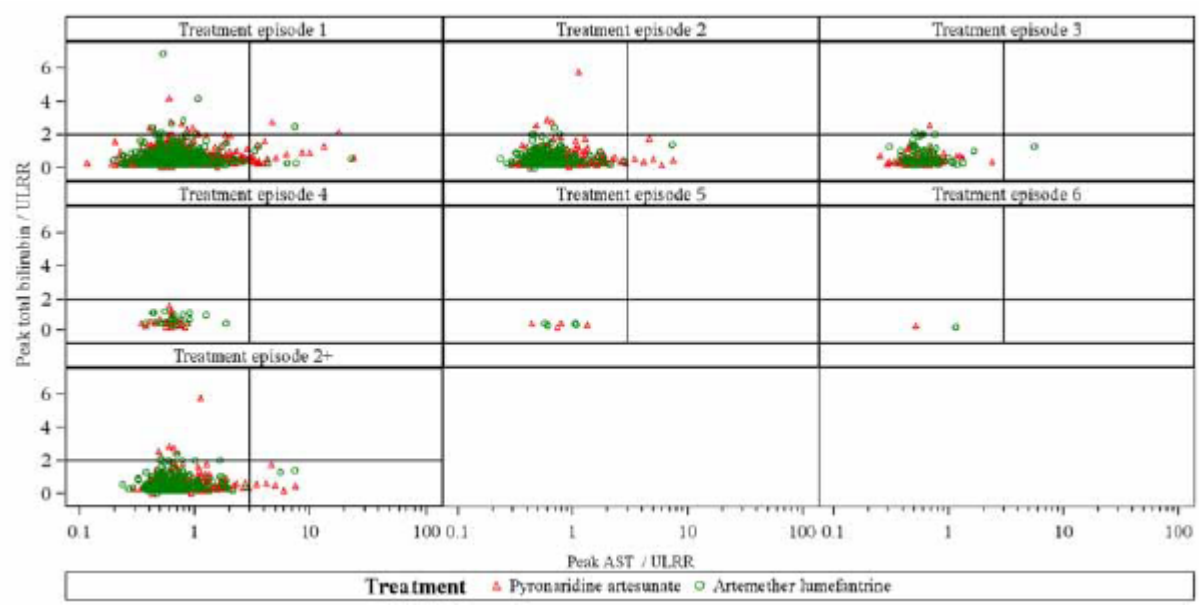


Figure 3 Scatter Plot of Peak Bilirubin versus Peak ALT ≥Day 7, by Treatment Episode (Overall Safety Population)

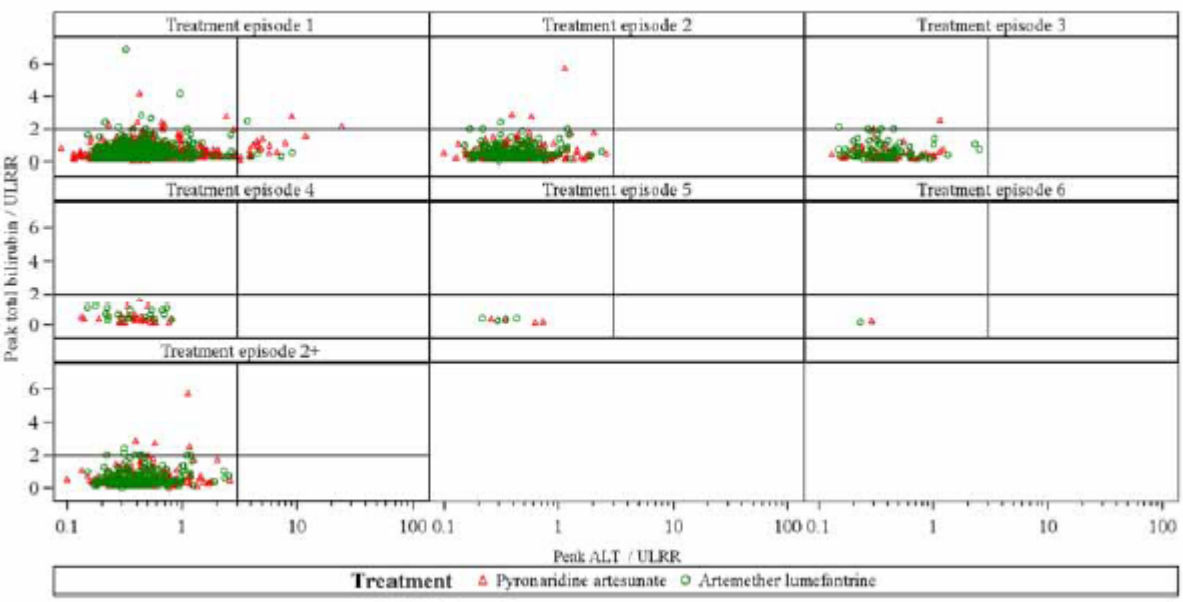
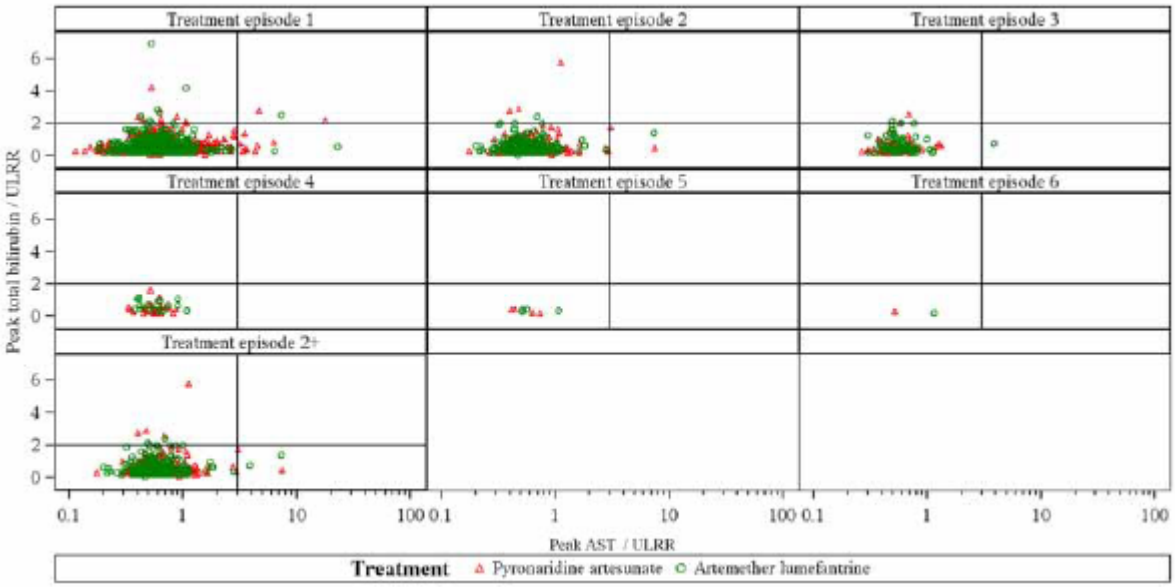
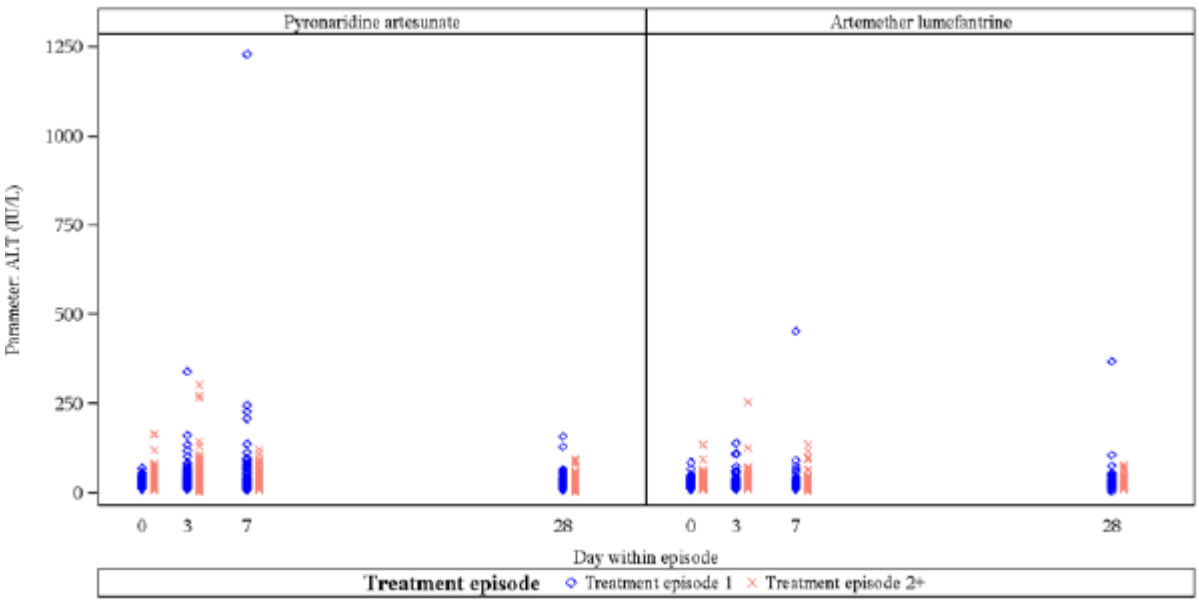


Figure 4: Scatter Plot of Peak Bilirubin versus Peak AST ≥Day 7, by Treatment Episode (Overall Safety Population)



Results from patients with 2 or more episodes were similar to 1 episode, indicating that the hepatotoxicity did not worsen with repeat administrations. For the repeat dose population, the scatter plot in Figure 5 shows that patients who had increases in ALT on first dosing tended to have lower ALT values on second exposure.

Figure 5 Scatter Plot of ALT Over Time, by Treatment Episode (Repeat Dose Safety Population)



Taking the repeat dose population, the proportions for patients using the worst post-dose values for the first treatment and any subsequent treatment there was no increase in significant ALT enzyme rises.

Table 29: Incidence of ALT Values Relative to the Normal Range, by Treatment Episode, Treatment and Time Point (Repeat Dose Safety Population)

Time point		Pyronaridine artesunate (N=316) n / total (%)	Artemether lumefantrine (N=238) n / total (%)
Treatment Episode 1			
Highest value post Day 0	ALT <=1.5 x ULN	298 / 314 (94.9)	229 / 238 (96.2)
	ALT >1.5 x ULN and <=3 x ULN	10 / 314 (3.2)	7 / 238 (2.9)
	ALT >3 x ULN and <=5 x ULN	3 / 314 (1.0)	0 / 238 (0.0)
	ALT >5 x ULN and <=10 x ULN	2 / 314 (0.6)	2 / 238 (0.8)
	ALT >10 x ULN	1 / 314 (0.3)	0 / 238 (0.0)
Treatment Episode 2+			
Highest value post Day 0	ALT <=1.5 x ULN	294 / 309 (95.1)	230 / 236 (97.5)
	ALT >1.5 x ULN and <=3 x ULN	12 / 309 (3.9)	5 / 236 (2.1)
	ALT >3 x ULN and <=5 x ULN	1 / 309 (0.3)	1 / 236 (0.4)
	ALT >5 x ULN and <=10 x ULN	2 / 309 (0.6)	0 / 236 (0.0)
	ALT >10 x ULN	0 / 309 (0.0)	0 / 236 (0.0)

No relationship between hepatotoxicity and time between treatment episodes was observed. Shift tables for ALT in the PA arm for worst post-dose value for episode 1 and episodes 2+ are shown in Table 30.

Table 30. Shift Table of ALT Categories from Pre-dose to the Worst Post-dose value, by Treatment Episode and Treatment (Overall Safety Population)

Treatment		Number (%) of patients: Day 0					
		Total	<1.5 x ULN	>1.5-<=3 x ULN	>3-<=5 x ULN	>5-<=10 x ULN	>10 x ULN
Treatment Episode 1							
Pyronaridine artesunate	Total	995 (100.0)	991 (99.6)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
	<1.5 x ULN	926 (93.1)	924 (92.9)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	>1.5-<=3 x ULN	46 (4.6)	45 (4.5)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	>3-<=5 x ULN	10 (1.0)	9 (0.9)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	>5-<=10 x ULN	10 (1.0)	10 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>10 x ULN	3 (0.3)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment Episode 2							
Pyronaridine artesunate	Total	304 (100.0)	299 (98.4)	4 (1.3)	1 (0.3)	0 (0.0)	0 (0.0)
	<1.5 x ULN	289 (95.1)	286 (94.1)	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)
	>1.5-<=3 x ULN	12 (3.9)	12 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>3-<=5 x ULN	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
	>5-<=10 x ULN	2 (0.7)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
	>10 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Patients were excluded from the study if they had an ALT/AST of >2 x ULN, but some patients did have raised values on Day 0 of the episode. These data show that, for episode 1, 4 patients had Day 0 values of >ULN, but ≤3 x ULN; 2 patients reverted to <1.5 x ULN, 1 patient remained within this category and 1 patient worsened to >3 x ULN, but ≤5 x ULN. For episodes 2+, 5 patients had values >1.5 x ULN on Day 0 of the episode, one of whom had an ALT of >3 x ULN, but ≤5 x ULN. This patient shifted to <1.5 x ULN during treatment while, of the 4 patients who had values >1.5 x ULN, but ≤3 x ULN, 2 patients shifted to <1.5 x ULN, 1 patient shifted to >3 x ULN, but ≤5 x ULN and 1 patient shifted to >5 x ULN, but ≤10 x ULN.

The number of patients with raised enzymes on Day 0 is very small, but does not indicate that raised levels at baseline necessarily are associated with a worsening of transaminases on treatment.

Detailed analysis of effect of retreatment

The SOH has reviewed the data for all patients who had a rise in ALT or AST > 1.5 x ULN in any episode. As the concern is about the effect of retreatment, only those patients who had more than one episode have been included. From the re-treated sub-analysis population, 33/316 (10.4%) patients had a rise of ALT/AST > 1.5 x ULN post treatment. Table 31 below shows the proportion of patients who had a raise in any episode as well as the number who had raises in more than one episode. Of note is that rises in AST were more common than ALT predominantly in episode 2. The percentage of patients with rises otherwise remained similar between episode 1 and 2.

Table 31: Summary of patients with ALT or AST rises >1.5 x ULN (or higher than baseline) post treatment

	N Treated	N with rises ALT ± AST (%)	N with rises ALT + AST (%)	ALT (%)	AST (%)
Episode 1	316	12 (3.8%)	9 (2.8%)	10 (3.2%)	11 (3.5%)
Episode 2	316	29 (9.2%)	11 (3.5%)	15 (4.7%)	24 (7.6%)
Episode 3	84	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)
Episode 4	28	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
> 1 episode	316	8 (2.5%)	5 (1.6%)	4 (1.3%)	8 (2.5%)
> 2 episodes*	84	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)
> 3 episodes	28	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*included in > 1 episode

A summary of these findings for individual patients was provided and case narratives were made available.

Among the patients who have been treated at least 2 times with PA and have reported at least one rise of ALT or AST > 1.5 x ULN, 5 patients had to be excluded from the analysis: 4 patients who already presented transaminase rise at D0 and 1 patient with a transaminase rise after quinine administration.

Among the 33 remaining patients, 79% of patients generally reported moderate transaminases rise <5N: grade 1, n=17 (52%); grade 2, n= 9 (27%); grade 3, n= 5 (15%); grade 4, n= 2 (6%).

One additional patient (2 year-old female patient) presented Hy's law with abdominal pain of moderate intensity at D7 after the 3rd PA administration (after 199 and 75 days between each PA administrations), which is a reason of protocol exclusion (additional case 21-0608 post-study analysis). The patient took once, 125 mg of paracetamol before the clinical visit. On D3, bilirubin was normal with ALT 1.5 x ULN and AST 2.4 x ULN. On D7, digestive parasitosis was suspected due to moderate hepatomegaly. Albendazole was administrated between D7-D10 and at D8, the patient presented ALT 13 x ULN, AST 20 x ULN, and

total bilirubin 3.2 x ULN. Complementary search did not reveal any virologic etiology. Even if chronology is also suspected for albendazole, Hy's law seems more likely due to PA administration. The child improved with observed normal values at D21.

Data regarding rechallenge are only informative for 23 cases:

- negative rechallenges occurred in 13 patients, sometimes several times.
- positive rechallenges occurred in 10 patients, generally without relevant worsening.

Hy's law cases

Overall among the 4200 patients exposed to pyronaridine-artesunate, there have been reported 4 confirmed cases of Hy's law without described confounding factors (including 2 cases with eosinophils rise), 1 confirmed case of Hy's law with confounding factor and 1 possible Hy's law case (case tabulation shown in assessment report for procedure X-0008).

Interval QT prolonged

ECG data were not specifically analysed in the repeat dose populations but the data would suggest that there is no increased risk of QTc changes or other ECG abnormalities with repeat dosing based on the overall alert signals:

Approximately a third of patients had a central review of ECGs with special attention to QTc which was reported with both Bazett and Fridericia corrections.

Prolonged ECG QT was reported for 53 patients (5.2%) in the PA arm and 62 patients (9.2%) in the AL arm during episode 1, for 20 patients (6.3%) in the PA arm and 14 patients (5.9%) in the AL arm during episode 2, for 5 patients (6.0%) in the PA arm and 3 patients (3.7%) in the AL arm during episode 3, and for 2 patients (7.1%) in the PA arm and no patients in the AL arm during episode 4. These AEs were reported based on the investigator's assessment at each study centre and not on the central ECG readings.

By body weight category, QTc prolongation was highest in the <20 kg category in both treatment arms, but lower in the PA arm than in the AL arm. A smaller number of patients had at least 1 ECG-related AE in episode 2. There were more QTc prolongations in the PA arm than in the AL arm during episode 3, but the overall number of patients in the episode was small.

For QTcB the mean change (median similar) in episode 1 between Day 2 and Day 0 was -2.8 msec for PA and +3.2 msec for AL; for episode 2 these values were +0.9 and 4.9 msec respectively.

For QTcF the mean change in episode 1 between Day 2 and Day 0 was +8.4 msec for PA and +19.2 msec for AL. For episode 2 these values were +9.3 and 18.3 msec respectively.

The key QTc alert parameters are shown below:

Table 32 : Measured QTc Alert Signals

	QTcB				QTcF			
	PA		AL		PA		AL	
Episode	1	2	1	2	1	2	1	2
ECGs reviewed	n=396	n=118	n=192	n=62	n=396	n=118	n=192	n=62
≤ 0 msec	49.5%	44.1%	39.6%	31.3%	32.6%	27.1%	15.6%	17.2%
>0 to <30 msec	35.1%	39.8%	37.0%	51.6%	43.9%	51.7%	46.9%	46.9%
30 to 60 msec	4.5%	6.8%	9.4%	4.7%	11.4%	11.9%	22.4%	20.3%
>60 msec	0.0%	0.0%	0.5%	0.0%	1.3%	0.0%	1.6%	3.1%
Post dose								
>450 msec	4.3%	5.9%	8.9%	9.4%	0.0%	0.8%	0.0%	3.1%
>480 msec	0.0%	0.0%	0.0%	1.6%	0.0%	0.0%	0.0%	1.6%
>500 msec	0.0%	0.0%	0.0%	1.6%	0.0%	0.0%	0.0%	0.0%

These data show that, despite of some changes > 30 msec from Day 0, there were very few patients who received PA who had a QTc >450 msec and none with a QTc >480 msec except for one isolated case in episode 3 (QTcB but not QTcF). For AL, QTcF was worse than PA and there appeared to be a slight worsening in episode 2.

Based on these data there appears to be no QTc issue with PA and no worsening on re-dosing and the profile remains non-inferior to AL.

There does not appear to be a relationship between the time of re-dosing with PA and increases in QTc.

Table 33 : Number (%) of patients with signal QTc values or signal QTc increase from Day 0 of actual episode, and Episode 2 with time between episodes (Central ECG reading; Primary safety population)

	Total	Time between actual and previous episode (days), n(%)				
	n (%)	28-60	61-90	>90	≤60	≤90
Treatment episode 1						
Patients dosed and ECG available	**396**	**NA**	**NA**	**NA**	**NA**	**NA**
QTc based on Bazett's formula						
Increase between highest post dose value and Day 0						
<= 0 msec (decrease)	196(49.5)					
>0 - <30 msec	139(35.1)					
30 - 60 msec	18(4.5)					
> 60 msec	0(0.0)					
Day 0 missing	43(10.9)					
Any post dose QTc > 450 msec	17(4.3)					
Any post dose QTc > 480 msec	0(0.0)					
Any post dose QTc > 500 msec	0(0.0)					
QTc based on Fridericia's formula						
Increase between highest post dose value and Day 0						
<= 0 msec (decrease)	129(32.6)					
>0 - <30 msec	174(43.9)					
30 - 60 msec	45(11.4)					
> 60 msec	5(1.3)					
Day 0 missing	43(10.9)					
Any post dose QTc > 450 msec	0(0.0)					
Any post dose QTc > 480 msec	0(0.0)					
Any post dose QTc > 500 msec	0(0.0)					
Treatment episode 2						
Patients dosed and ECG available	**118**	**39**	**22**	**57**	**39**	**61**
QTc based on Bazett's formula						
Increase between highest post dose value and Day 0						
<= 0 msec (decrease)	52(44.1)	13(33.3)	5(22.7)	34(59.6)	13(33.3)	18(29.5)
>0 - <30 msec	47(39.8)	16(41.0)	16(72.7)	15(26.3)	16(41.0)	12(52.5)
30 - 60 msec	8(6.8)	1(2.6)	0(0.0)	7(12.3)	1(2.6)	1(1.6)
> 60 msec	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Day 0 missing	11(9.3)	9(23.1)	1(4.5)	1(1.8)	9(23.1)	10(16.4)
Any post dose QTc > 450 msec	7(5.9)	2(5.1)	2(9.1)	3(5.3)	2(5.1)	4(6.6)
Any post dose QTc > 480 msec	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Any post dose QTc > 500 msec	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
QTc based on Fridericia's formula						
Increase between highest post dose value and Day 0						
<= 0 msec (decrease)	32(27.1)	9(23.1)	4(18.2)	19(33.3)	9(23.1)	13(21.3)
>0 - <30 msec	61(51.7)	16(41.0)	16(72.7)	29(50.9)	16(41.0)	32(52.5)
30 - 60 msec	14(11.9)	5(12.8)	1(4.5)	8(14.0)	5(12.8)	6(9.8)
> 60 msec	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Day 0 missing	11(9.3)	9(23.1)	1(4.5)	1(1.8)	9(23.1)	10(16.4)

Any post dose QTc > 450 msec	1(0.8)	0(0.0)	1(4.5)	0(0.0)	0(0.0)	1(1.6)
Any post dose QTc > 480 msec	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Any post dose QTc > 500 msec	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Although there seems no evidence for an increased safety risk with PA re-dosing based on ECG findings, a dedicated QT/QTc study according to ICH E14 guideline, has not been performed.

Other *AE in PA repeated dosage*

Related adverse events occurring in at least one patient in any subpopulation from the repeat dose safety populations, for episodes 1-3 are shown in the following table:

Table 34: Incidence of adverse events occurring in ≥1% of patients considered to be study drug related, by episode (Repeat dose safety populations)

	Repeat	Subpop1	Subpop2	Subpop3
Primary system organ class	**All**	**<60 days**	**<90 days**	**> 90 days**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Treatment episode 1				
Patients dosed	**316 (100.0)**	**173 (100.0)**	**236 (100.0)**	**80 (100.0)**
At least one adverse event	**63 (19.9)**	**36 (20.8)**	**50 (21.2)**	**13 (16.3)**
Blood and lymphatic system disorders	13 (4.1)	8 (4.6)	10 (4.2)	3 (3.8)
Neutropenia	7 (2.2)	4 (2.3)	5 (2.1)	
Anaemia	2 (0.6)	2 (1.2)		2 (2.5)
Monocytosis	5 (1.6)	2 (1.2)	3 (1.3)	2 (2.5)
Eye disorders				1 (1.3)
Conjunctivitis				1 (1.3)
Gastrointestinal disorders	15 (4.7)	8 (4.6)	12 (5.1)	3 (3.8)
Vomiting	9 (2.8)	4 (2.3)	7 (3.0)	2 (2.5)
Abdominal pain	6 (1.9)	4 (2.3)	5 (2.1)	2 (2.5)
Hepatobiliary disorders				1 (1.3)
Drug-induced liver injury				1 (1.3)
Hyperbilirubinaemia				1 (1.3)
Infections and infestations			3 (1.3)	
Bronchitis			3 (1.3)	
Investigations	33 (10.4)	18 (10.4)	24 (10.2)	9 (11.3)
Electrocardiogram QT prolonged	19 (6.0)	14 (8.1)	16 (6.8)	3 (3.8)
Alanine aminotransferase increased	11 (3.5)	3 (1.7)	5 (2.1)	6 (7.5)
Aspartate aminotransferase increased	10 (3.2)	3 (1.7)	5 (2.1)	5 (6.3)
Treatment episode 2				
Patients dosed	**316 (100.0)**	**173 (100.0)**	**236 (100.0)**	**80 (100.0)**
At least one adverse event	**48 (15.2)**	**27 (15.6)**	**38 (16.1)**	**10 (12.5)**
Blood and lymphatic system disorders	9 (2.8)	4 (2.3)	8 (3.4)	1 (1.3)
Neutropenia		2 (1.2)		1 (1.3)
Thrombocytopenia	4 (1.3)	2 (1.2)	3 (1.3)	1 (1.3)

	Repeat	Subpop1	Subpop2	Subpop3
Primary system organ class	**All**	**<60 days**	**<90 days**	**> 90 days**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal disorders	7 (2.2)	5 (2.9)	7 (3.0)	
Vomiting	4 (1.3)	4 (2.3)	4 (1.7)	
Investigations	30 (9.5)	16 (9.2)	20 (8.5)	10 (12.5)
Electrocardiogram QT prolonged	20 (6.3)	11 (6.4)	15 (6.4)	5 (6.3)
Aspartate aminotransferase increased	8 (2.5)	4 (2.3)	4 (1.7)	4 (5.0)
Alanine aminotransferase increased	4 (1.3)	2 (1.2)		2 (2.5)
Blood creatinine increased	2 (0.6)	2 (1.2)		
Metabolism and nutrition disorders	2 (0.6)	2 (1.2)		
Hypercreatininaemia	2 (0.6)	2 (1.2)		
Nervous system disorders	2 (0.6)	1 (0.6)		
Somnolence	2 (0.6)	1 (0.6)		
Treatment episode 3				
Patients dosed	**84 (100.0)**	**66 (100.0)**	**78 (100.0)**	**6 (100.0)**
At least one adverse event	**11 (13.1)**	**9 (13.6)**	**10 (12.8)**	**1 (16.7)**
Blood and lymphatic system disorders	2 (2.4)	2 (3.0)	2 (2.6)	
Anaemia	1 (1.2)	1 (1.5)	1 (1.3)	
Neutropenia	1 (1.2)	1 (1.5)	1 (1.3)	
Infections and infestations	1 (1.2)	1 (1.5)	1 (1.3)	
Bronchitis	1 (1.2)	1 (1.5)	1 (1.3)	
Rhinitis	1 (1.2)	1 (1.5)	1 (1.3)	
Investigations	5 (6.0)	3 (4.5)	4 (5.1)	1 (16.7)
Electrocardiogram QT prolonged	4 (4.8)	2 (3.0)	3 (3.8)	1 (16.7)
Blood creatinine increased	1 (1.2)	3 (4.5)	1 (1.3)	
Metabolism and nutrition disorders	4 (4.8)	2 (3.0)	4 (5.1)	
Hypercreatininaemia	4 (4.8)	1 (1.5)	4 (5.1)	
Skin and subcutaneous tissue disorders	1 (1.2)	1 (1.5)	1 (1.3)	
Dermatitis allergic	1 (1.2)	1 (1.5)	1 (1.3)	

Patients dosed >90 days after the previous episode were the smallest population and thus individual events reflected a higher percentage compared with the other subpopulations; nonetheless there was no evidence that the general pattern of adverse events changed according to the time following the previous dosing episode.

Safety in special populations

Children < 20kg

The overall percentage of subjects with treatment-emergent AEs by weight category was similar in the PA and all comparators groups. For the majority of treatment-emergent AEs, no notable differences in incidence were observed by weight group.

Adverse events occurred with a similar incidence between PA and AL for episode 1 but were more frequent in both treatment groups for patients <20 kg the main differences being in infections and

infestations and investigations. In the latter there was a difference between PA and AL whereby raised transaminases were more common for PA and QTc prolongation was more common for AL. The incidence of adverse events in re-treatment episode was lower than episode 1 for AL but similar for PA.

The proportions of treatment related adverse events were also similar between the treatment group and between the episodes again being more frequent in the < 20 kg weight group and here there was no difference in incidence between 1st and subsequent episodes. In episode 1, neutropenia was slightly more frequently related to treatment in the < 20 kg group and QTc prolongation as assessed by the investigator was more common in the lighter group. QTc prolongation was highest in the <20 kg category. A smaller number of patients had at least 1 ECG-related AE in episode 2. Transaminase rises were considered related in similar proportions across the treatment groups and weights except for the AL group ≥20 kg where it was the least frequently reported. Vomiting was more frequent in the PA <20 kg group than the others. In episode 2 the incidence of related adverse events was less than in episode 1 and in episode 3 single cases meant that the incidence was distorted in percentage terms but there was no obvious trend to increased events in either weight range. Episode 4 only had 1 case each of related QTc prolongation reported for PA.

Post-marketing data

Based on the parallel review of the last PSUR data (cut-off date 31 October 2014), the SOH stated that no serious adverse events have been newly reported considering the 4650 patients who have been cumulatively exposed patients with pyronaridine-artesunate during clinical experience. Among these 4650 patients, 748 patients have been exposed twice, 403 exposed three times and 177 exposed four times. Even if all data have not been analysed yet serious adverse events are reported directly to the SOH.

Table 35. Experience on retreatment in a 1 year period

Number of exposed patients to Pyramax:	Cut-off date 31 October 2013 (II02 and X08 procedures)	Cut-off date 31 October 2014 (6th PSUR)
Cumulative exposure at least once including:	1015	1377
Cumulative exposure at least twice	316	748
Cumulative exposure at least 3 times	84	403
Cumulative exposure at least 4 times	28	177

2.5.1. Discussion on clinical safety

Due to the hepatotoxic characteristics of pyronaridine, combined with potential accumulation in the liver and no data on the safety of repeated dosing, the indication of Pyramax has been limited to a single treatment course in any given patient. At time of initial scientific opinion, it was proposed that Pyramax be dispensed at facilities equipped to undertake the required liver function monitoring and only in areas with low malaria transmission and with evidence of resistance to artemisinin combination treatments. The risk of liver toxicity with increases in liver transaminases was also framed with a contra-indication in case of underlying hepatic injury or significant liver function test abnormalities, and recommendation to perform liver function tests both before and after Pyramax treatment course. Moreover the SOH was recommended to conduct a mechanistic trial regarding liver toxicity.

For the current extension of indication application, longitudinal study (SP-C-013-11) allowed Pyramax to be tested over a number of malaria seasons in patients presenting with uncomplicated malaria. In the present study both a granule as a tablet formulation are used. The granule formulation has been developed to ease dosing in smaller children (see parallel regulatory procedure X/0008). Patients with a

bodyweight ≥20 kg received the tablet formulation, and thus where results have been presented by body weight, the focus of the assessment is on the effects of repeated dosing in patients with a bodyweight ≥20kg.

For the tablet formulation the rate of all treatment emergent AEs decreases with repeated dosing. The rate of all treatment related AEs is similar between the first treatment episode and subsequent treatment episodes. There was no trend to more AEs with re-treatment or with the time between treatments in the PA arm between episodes 1, 2, and 3.

Hepatotoxicity

The primary safety endpoint for this sub-study was defined as the occurrence of hepatotoxicity events (with event being defined as ALT >5 x ULN or Hy's law [ALT or AST >3 x ULN and total bilirubin >2 x ULN]) at any post-dose time point.

There is evidence of increased liver toxicity as compared to AL, which is in line with the findings from the studies assessed during the initial application. The hepatotoxic properties of pyronaridine are known and are adequately described in the SmPC where a clear warning is included in section 4.4.

The main question is whether hepatotoxic events increase with repeated dosing. For this there is no evidence as the incidence of hepatotoxicity-related adverse events is marginally lower with the second treatment episode compared to the first treatment episode (for the tablet formulation). Do note that patients were excluded from (re) treatment if they had liver abnormalities as Pyramax remains contra-indicated in patients with underlying hepatic injury or significant liver function test abnormalities or patients who experienced significant increase in liver transaminases related to the administration of pyronaridine.

Hepatotoxicity events, based on raw values (actual measurements), after Day 0, were reported for 13 patients in relation to the first treatment episode and for 2 patients regarding the second treatment episode. No hepatotoxicity events were reported for any patients during episodes 3, 4, 5, 6, 7, 8 or 9. The 2 events during episode 2 in the PA arm were reported 28 to 60 days and >90 days after the first episode, respectively. Based on the post-dose worst case per episode, the estimated hepatotoxicity event rate for initial administration was 1.3% and 0.5% for repeat administrations. The estimated difference in the event rate of repeat versus initial administration was -0.8% with a 95% CI upper limit of 0.0.

Further on, the SOH provided a full description of each individual case of re-challenge (for each patient who presented a transaminase rise from 1.5 ULN either regarding ALT or AST). Data obtained did not identify a signal towards a significant worsening in case of rechallenge, including if re-introduction occurs in a short delay. Indeed, no higher risk of hepatotoxicity of pyronaridine after repeated dosing than single dosing emerged from the review of the 23 cases of re-challenges. The rise of transaminase resolves in the month for all patients and generally with no clinical impact (except for the new case of Hy's law which only reported abdominal pain at first sign which conducts to diagnose a hepatomegaly without pain). Furthermore, patients who experience one episode of transaminase rise do not necessarily experience a transaminase rise on any subsequent dosing episode, thus suggesting that there are no lasting effects from that exposure, even when the repeat dosing occurs during the pyronaridine 5 x half-life period. These data are re-assuring, with following caveat:

- The data on retreatment rely on a limited number of patients
- retreatment was not allowed in case of significant liver abnormalities in previous episodes (exclusion criteria from retreatment: transaminase rise more than 5xULN or Hy's law criteria (ALT>5xULN and total bilirubin >2xULN)

- HCV, HBV, HIV co-infection, patients with ALT values >2ULN were exclusion criteria (therefore the potential for increased risk of hepatotoxicity based on the liver injury and/or concomitant toxic medication is not documented)

Moreover, the SOH proposed to delete systematic liver testing and therefore is proposing to delete the current contra-indication "significant increase in liver transaminases related to the administration of pyronaridine" but revisited the contra-indication with introduction of the terms "known" in the statement "underlying hepatic injury or *known* significant liver function test abnormalities". The input of expert group (SAG) on anti-infectives was consulted to discuss the conditions under which retreatment could be safely considered, in endemic countries (see below).

Other safety findings

Considering measured haematology values, there were no substantive differences between PA and AL or trends in any of the haematological factors including haemoglobin or neutrophils (which tended to fall), eosinophils (which tended to rise being higher at Day 28) or platelets (which rose on treatment) and no trend for differences with re-treatment.

The number of patients with signal QTc values or signal QTc increases from Day 0 were similar between the PA and AL arm, with patients in the AL arm showing a slightly larger increase between highest post dose value and Day 0. There was no clear evidence of an increased risk of QTc prolongation with repeated dosing, in particular considering the data post episode 1 and post episode 2. There are only very limited patients with ECG available who were treated for a 3rd or 4th episode making this data difficult to interpret.

Although there seems no evidence for an increased safety risk with PA re-dosing based on ECG findings, a dedicated QT/QTc study according to ICH E14 guideline, could eventually be be considered (apart from ongoing pharmacovigilance). A cautionary statement is appearing in SmPC, section 4.4, regarding its use in at risk patients, ie. those with congenital prolongation of QTc interval, hypokalaemia, dehydration, cardiac arrhythmia, heart failure, treated concomitantly with other drugs that can block potassium channels, and those recently treated with medicinal products with long elimination half-life and known to prolong the QTc interval that may still be circulating at the time Pyramax treatment course is commenced.

Additional expert consultation

To further clarify the appropriate use of Pyramax, allowing re-treatment, an expert meeting was convened. Based on the current data (as derived from clinical data in children $\geq$5 kg to adults), it was questioned what level of reassurance in terms of hepatotoxicity had been gained. It was also questioned to what extent the data accumulated are compatible with the use of the drug in asymptomatic patients without systemic liver testing (i.e. while patients in the study could only be treated if ALT<2ULN) and if extrapolation beyond the study population would be possible. Experts asserted that there is indeed sufficient evidence to use the medicinal product in the proposed way- i.e. in asymptomatic patients without systematic liver testing-, also considering a broader population (e.g. co-infection, having experienced transaminase rise more than 5ULN or Hy's law after the initial or previous treatment) provided that an effective RMP be put in place, including appropriate pharmacovigilance measures and the commitment of a phase IV study to be carried out. The experts were also united in their view that routine liver function testing would not be possible in the intended clinical setting. Also, in view of the short treatment duration, no stopping rules can be formulated for emerging signs /symptoms of liver injury (since the course would have stopped already in anyway). This contrasts though to treatment emerging anaphylaxis (requiring immediate cessation of therapy). Also, as stated in the Product

Literature, treatment should not be started in those with known underlying hepatic injury. Thus, retreatment in the affected community would therefore be permitted unless the patient had history of anaphylaxis, clinical jaundice or otherwise known severe liver disease (decompensated cirrhosis, Child-Pugh stage 3 or 4).

With reference to the proposed study, it should contain the following elements:

a. Population: All those with malaria requiring oral therapy to be included:

- all age groups to be represented (from 5kg body weight onwards)

- co-infection: HIV infected and those suffering chronic hepatitis (B, C). Also, in view of high prevalence of hepatitis E in Africa and its unsure role in causing chronic liver disease in those co-infected with HIV, serological screening for hepatitis E should be included in the protocol.

- liver function tests: patients with abnormal liver function tests allowed, but with exclusion of those presenting with decompensated cirrhosis

b. Repeat use: to be included

c. Drug-drug interaction: should be investigated for all cases in which DDI has a potential; particular focus to be placed on interaction with P450 cytochrome enzymes and potential mitochondrial toxicity.

d. Nutritional status: to be examined, with height/weight data to be collected for population < 20 kg

e. Decision tool (as proposed): to be validated

f. Testing: standard biochemical panels to be used, to determine whether clinical testing misses significant numbers with cirrhosis

2.5.2. Conclusions on clinical safety

Overall, safe repeated courses Pyramax Tablets considered in a broader population (as compared to the restrictive conditions in study SP-C-013-11) and without systematic liver function testing is justified, provided an effective RMP be put in place, including appropriate pharmacovigilance measures and the commitment of a phase IV study to be carried out. To this purpose, the SOH's proposal for the phase IV study can be overall agreed. Moreover, the SmPC reflects the limitations of the data and includes specific warnings.

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

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

Post-opinion measure (s)	Motivation
Proposed post-opinion measure with proposed classification:	Post-registration study protocol to derive further reassurance on the use of PYRAMAX under enlarged conditions (retreatment, co-infections, no systematic liver testing, very small children [notably <1 year of age] with particular issues on malnutrition) Planned to start in January 2016 Category 3

* Classification: Annex II (specific obligations; obligations), RMP

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The SOH submitted an updated RMP, version 12.1 following the PRAC meeting, to improve the compatibility with guidance and address comments in the rapporteur's assessment report.
The CHMP endorsed the Risk Management Plan version 12.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Increases in liver transaminases (including rare Hy's Law cases) Exacerbation of anaemia Neutropenia Vomiting Diarrhoea Interaction with drugs metabolised through CYP2D6 or via P-gp efflux
Important potential risks	Severe Malnutrition (impact on hepatotoxicity of pyronaridine in relation to GSH stock depletion) Use in pregnancy and lactation • Passage into breast milk • Embryotoxicity/teratogenicity Neurotoxicity Prolongation of QT and/or bradycardia Induction of resistance Tissue accumulation of pyronaridine with inflammation and degenerative changes Skin discolouration Drug interactions with TB or HIV agents metabolised via CYP2D6 pathways
Important missing information	Hepatotoxicity in patients with suspected cumulative risk factors: repeat course of PYRAMAX notably with short delay of re-introduction, malnutrition, co-infections (HBV, HCV, HIV), co-administration of drugs to be associated with mitochondrial toxicity (i.e valproate, antiretroviral drugs), other hepatic underlying conditions (i.e. ethanol intoxication, hepatic steatosis), increased liver transaminases before administration, co-administration of paracetamol, use of herbal medicines. Safety in very young children (i.e. infants <10 kg notably 5-8 kg), including repeated dose Off label use in infants under 5 kg in weight Safety in elderly patients HIV/AIDs infection Significant anaemia (Hb < 8 g/dL)

Summary of safety concerns	
	Haemoglobinopathies (e.g. thalassaemia, sickle cell and G6PD deficiency) Patients with hepatic, renal, or cardiac impairment

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
SP-C-013-11 (WANECAM) A Phase IIIb/IV comparative, randomised, multi-centre, open label parallel 3-arm clinical study to assess the safety and efficacy of repeated administration of pyronaridine-artesunate, dihydroartemisinin-piperaquine or artemether-lumefantrine or artesunate-amodiaquine over a two-year period in children and adult patients with acute uncomplicated *Plasmodium* sp. malaria. Category 3	To compare the efficacy and the safety of repeated ACT therapy over a period of 2 years (PA or DHA-piperaquine will be compared to either AS-AQ or AL) in children and adults	Increases in liver transaminases (including rare Hy's Law cases) Exacerbation of anaemia Neutropenia Prolongation of QT and/or bradycardia Induction of resistance Safety in very young children (ie. infants <10 kg notably 5-<8 kg) in weight, including repeated dose Significant anaemia (patients with Hb < 8 g/dL)	Recruitment complete and in follow up	Final CSR due 31 September 2016
SP-PV-001-12 Pregnancy Registry Category 3	Monitor all pregnancies and their outcomes	Use in pregnant and lactating women – risk of embryotoxicity/teratogenicity	Ongoing	Annual updates Final report due 31 December 2015
SP-C-021-15 Phase IIIb/IV Cohort Event Monitoring study to evaluate the safety in patients after the local registration of PYRAMAX Category 3	To assess the safety of PYRAMAX in patients to include those with underlying liver function abnormalities, co-morbid conditions, such as HIV, and also infants (<1 year of age)	Increases in liver transaminases (including rare Hy's Law cases) Exacerbation of anaemia Interaction with metabolised through CYP2D6 or via P-gp efflux Severe Malnutrition (impact on hepatoxicty of pyronaridine in relation to GSH stock depletion) Hepatotoxicity in patients with suspected cumulative risk factors: repeat course of PYRAMAX notably with short delay of re-introduction, malnutrition, co-infections (HBV, HCV, HIV), co-administration of drugs to be associated with mitochondrial toxicity (i.e valproate, antiretroviral drugs), other hepatic underlying conditions	expected to start by 30 January 2016	Final CSR due 30 September 2018

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
		(i.e. ethanol intoxication, hepatic steatosis), increased liver transaminases before administration, co-administration of paracetamol, use of herbal medicines Safety in very young children (i.e. infants <10 kg notably 5-8 kg), including repeated dose Safety in elderly patients HIV/AIDs infection Significant anaemia (Hb < 8 g/dL)		
SP-C-018-13 Study: Randomized, open-label trial of the safety, tolerability and efficacy of primaquine against relapse when combined with pyronaridine tetraphosphate-artesunate or dihydroartemisinin-piperaquine phosphate for radical cure of acute Plasmodium vivax malaria in soldiers Category 4	Evaluate the safety, tolerability and efficacy of primaquine against relapse when combined with pyronaridine tetraphosphate-artesunate or dihydroartemisinin-piperaquine phosphate for radical cure of acute Plasmodium vivax malaria in soldiers in Indonesia	*Plasmodium vivax malaria* in adults	Recruitment complete and in follow up	Final CSR due 31 December 2015
SP-C-019-14 Study: Monitoring and evaluation of the therapeutic efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria in western Cambodia, an area of artemisinin-resistant falciparum malaria Category 4	Monitor efficacy and safety in adults treated with tablets in Cambodia	Induction of resistance	Ongoing	Final CSR due 31 December 2015
SP-C-020-15 Study: Pyronaridine-artesunate and artemether-lumefantrine for the treatment of paediatric uncomplicated *falciparum* malaria in Western Kenya Category 4	To assess the safety and efficacy of the paediatric formulation of PYRAMAX compared to that of Artemether-Lumefantrine	Significant anaemia (Hb < 8 g/dL)	Recruiting	Final CSR due 31 December 2017

Risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Increases in liver transaminases(including Hy's Law cases)	Information in sections 4.2, 4.3, 4.4, 4.8, 5.3 of the SmPC related to hepatic restriction conditions and precautious recommendations. Also in Section 4.8, advice on the effect of Pyramax on transaminases in Caucasians will be amended.	None.
Exacerbation of anaemia	Information in sections 4.4 and 4.8 of the SmPC	None
Neutropenia	Information in section 4.2 and 4.4 of the SmPC	None
Vomiting	Information in sections 4.4 and 4.8 of the SmPC	None
Diarrhoea	Information in sections 4.4 and 4.8 of the SmPC	
Interaction with medication metabolised through CYP2D6 or via P-gp efflux	Information in sections 4.5 and 5.2 of the SmPC	None
Important Potential Risks		
Severe Malnutrition	Information in sections 4.4 and 5.1 of the SmPC	None
Use in pregnant and lactating women	Information in sections 4.4, 4.6 and 5.3 of the SmPC	None
Neurotoxicity	Information in section 5.3 of the SmPC	None
Prolongation of QT and/or bradycardia	Information in Section 4.4 and 4.8 of the SmPC	None
Induction of resistance	Information in section 5.1 of the SmPC	None
Tissue accumulation of pyronaridine with inflammation and degenerative changes	Information in section 5.3 of the SmPC	None
Skin discolouration	Information in section 5.3 of the SmPC	None
Drug interactions with TB or HIV agents metabolised via CYP2D6 pathways	Information in sections 4.5 and 5.2 of the SmPC	None
Missing Information		
Hepatotoxicity in patients with suspected cumulative risk factors	Warnings about the lack of information on repeat dosing are provided in sections 4.4 of the SmPC	None
Safety in very young children (ie. infants <10 kg notably 5-8 kg) including repeated dose	Information in section 4.2, 5.3 of the SmPC	None
Off label use in infants under 5 kg in weight	Information in section 4.1, 4.2, 5.1 of the SmPC	None
Safety in elderly patients	Section 4.2 indicates the lack of information and caution in these patients	
HIV/AIDs infection	Section 4.4 indicates the lack of information and caution in these patients	None
Significant anaemia (patients with Hb < 8 g/dL)	Information in section 4.4 and 4.8 of the SmPC	None
Haemoglobinopathies	None	None
Patients with hepatic, renal, or cardiac impairment	Information in Sections 4.2 and 4.3 of the SmPC regarding hepatic impairment Caution with regard to moderate renal impairment is provided in Section 4.2, 4.4 and 5.2. No special precautions are considered to be required for cardiac impairment	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the Scientific Opinion Holder took the opportunity to implement minor editorial and template-related changes in the annexes.

2.7.1. User consultation

Not applicable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Pyramax tablets are indicated in the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in adults and children weighing 20 kg or more, in areas of low transmission with evidence of artemisinin resistance. Pyramax is to be used only as a single treatment course in any given patient.

Results of the ongoing study SP-C-013-11 were submitted to amend the Summary of Product characteristics (SmPC), allowing repeat courses of PA to treat recurrent malaria episodes. Efficacy was evaluated as a secondary objective as the main focus of this study is on the safety of repeated dosing, specifically relating to hepatotoxicity.

As regards the issue of retreatment, the efficacy has been substantiated through the overall amount of data provided by study SP-C-013-11 in children above 20 kg and adults, with no particular signal towards a downgraded level of efficacy over time.

Uncertainty in the knowledge about the beneficial effects

At the time of the analysis of the 1015 patients treated with Pyramax and presented in this variation, there were 316 patients treated for 2 or more episodes and 83 patients treated with Pyramax on 3 or more occasions; with 81 patients treated with at least 3 times with AL. These data, although reassuring, are limited, and will be further updated when all data from study 213 are available.

Risks

Unfavourable effects

The most important identified risk with Pyramax concerns the hepatotoxicity. Mechanistic studies show this to be dependent on the intracellular glutathione level or the glutathione redox cycle and may be caused by oxidative damage. The suggested potential dose-dependent hepatotoxicity of pyronaridine could be linked, as paracetamol, to the formation of a hepatotoxic reactive metabolite which could be detoxified by glutathione (GSH). In the setting of a depletion of glutathione, inhibition of mitochondrial respiration occurs, causing cytolytic hepatitis.

To date, among a total of 4200 patients exposed to pyronaridine-artesunate, there have been a limited number (n=6) of reported Hy's law cases of which 4 confirmed cases without confounding factors. Mostly cases were asymptomatic and all resolved.

Uncertainty in the knowledge about the unfavourable effects

The main question is whether hepatotoxic events increase with repeated dosing. For this, there is no evidence as the incidence of hepatotoxicity-related adverse events is marginally lower with the second treatment episode compared to the first treatment episode.

Furthermore, patients who experience one episode of transaminase rise do not necessarily experience a transaminase rise on any subsequent dosing episode, thus suggesting that there are no lasting effects from that exposure, even when the repeat dosing occurs during the pyronaridine 5 x half-life period.

These data are re-assuring, with following caveat:

- The data on retreatment rely on a limited number of patients
- retreatment was not allowed in case of significant liver abnormalities in previous episodes (exclusion criteria from retreatment: transaminase rise more than 5xULN or Hy's law criteria (ALT>5xULN and total bilirubin >2xULN)
- HCV, HBV, HIV co-infection, patients with ALT values >2ULN were exclusion criteria (therefore the potential for increased risk of hepatotoxicity based on the liver injury and/or concomitant toxic medication is not documented)

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Pyramax has been administered to patients who have had repeated episodes of malaria and has been shown to be similarly effective and well tolerated on repeat dosing as for first administration with repeat dosing intervals as short as 28 days. Where transient ALT elevations occurred, the adverse event profile was similar with repeat administration for both adults and children. The significance of these findings need however to be placed into context of restricted inclusion /exclusion criteria applying to study SP-C-013-11.

Benefit-risk balance

Overall, based on the data available so far, the risk–benefit balance for the extension of indication application, allowing retreatment with Pyramax, is positive provided that an effective RMP be put in place, including appropriate pharmacovigilance measures and a commitment of a phase IV study to be carried out, in order to undertake enhanced real-life safety surveillance under enlarged conditions (retreatment, co-infection, no systematic liver testing).

Discussion on the Benefit-Risk Balance

Pyronaridine/artesunate is a new ACT that was demonstrated in Phase III studies to be at least as effective as AL and MQ + AS in the treatment of acute uncomplicated *P. falciparum* in children and adults and at least as effective as chloroquine in the treatment of acute uncomplicated *P. vivax* malaria in

children and adults. In addition, a Phase III paediatric study showed that PA is a good alternative to AL for the treatment of infants and children with acute uncomplicated P. falciparum malaria.

Due to hepatotoxicity, ascribed to pyronaridine, the use of Pyramax has been restricted to a single treatment course in any give patient (with appropriate liver tests monitoring), and confined to areas of low transmission with evidence of artemisinin resistance.

A repeat-dose longitudinal study (SP-C-013-11) has been undertaken in three West African countries which allowed Pyramax to be tested over a number of malaria seasons in patients presenting with uncomplicated malaria. An analysis of this study addresses safety and efficacy of repeat dosing: 1015 patients were treated with Pyramax tablets and granules for oral suspension; of the 622 patients weighing ⩾20 kg, 188 (30%) received at least one further treatment and, of these, 25% had a second or more re-treatment. Reasons for non-inclusion into the study or non- retreatment were complicated malaria or hyperparasitaemia or significantly raised liver enzymes as well as co-morbidities such as HIV, hepatitis, or severe malnutrition. Efficacy findings were similar to those in pivotal trials and were maintained with repeated treatment episodes. Pyramax seemed well tolerated during repeat course administration. Data obtained did not identify a signal towards a significant worsening in case of rechallenge, including if re-introduction occurs in a short delay. In order to get further assurance on hepatic safety, patients previously excluded or poorly represented in the clinical studies will be included in a pharmacovigilance study being conducted in endemic areas.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Scientific Opinion, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of the indication to remove restrictions on repeated courses of treatment in any patient and use only in areas of low transmission with evidence of artemisinin resistance. Consequently, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated in accordance. In addition, the Applicant took the opportunity to implement minor editorial and template-related changes in the annexes. A revised RMP version 12.1 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, labelling, Package Leaflet and to the Risk Management Plan (RMP).