EU Risk Management Plan for Pyronaridine Tetraphosphate Artesunate

RMP version to be assessed as part of this application:

RMP Version number: 18.2

Name	Job Title or Role	Electronic Signature and Date
Report prepared by [redacted]	[redacted]	[redacted]
Approved by: Robert M Miller	Qualified Person for Pharmacovigilance (QPPV) and Pyramax Medical Oversight for Shin Poong Pharmaceuticals	[redacted]
Approved by [redacted]	[redacted]	[redacted]

Table of content

Part I: Product(s) overview

Table Part I.1. Product(s) overview

Active substance(s) **(INN or common name)**	Pyronaridine Tetraphosphate Artesunate
Pharmacotherapeutic group(s) (ATC Code)	P01BF06
Marketing Authorisation Holder	Shin Poong Pharmaceutical Co. Ltd
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	PYRAMAX®
Marketing authorisation procedure	EU-M4all formerly EU Article 58 of Regulation (EC) No. 726/2004.
Brief description of the product	Chemical class: artemisinin and derivatives, combinations (ACTs)
	Pyronaridine tetraphosphate and artesunate (PYRAMAX) tablets are immediate release, orange, round, film-coated tablets. On each surface of the tablet, "PM" or "SP" is engraved, respectively. Each tablet contains 180 mg of pyronaridine tetraphosphate and 60 mg of artesunate. They contain not less than 90.0% and not more than 110.0% of $C_{29}H_{32}ClN_5O_2 \bullet 4H_3PO_4$ and not less than 90.0% and not more than 110.0% of $C_{19}H_{28}O_8$. Pyronaridine tetraphosphate and artesunate (PYRAMAX) granules for oral suspension are orange coloured granules enclosed in a sachet. Each sachet of granules contains 60 mg of pyronaridine tetraphosphate and 20 mg of artesunate. Each sachet contains not less than 93.0% and not more than 107.0% of $C_{29}H_{32}ClN_5O_2 \bullet 4H_3PO_4$ and not less than 90.0% and not more than 107.0% of $C_{19}H_{28}O_8$. Fixed dose combinations of artesunate and pyronaridine tetraphosphate have been used from Phase II onwards. The Phase II and Phase III clinical studies used a polyethylene glycol-based formulation. The commercial formulation for tablets and granules is based on a standard fluid bed granulation process. <u>Pyronaridine Mode of Action</u> Initial studies indicated that pyronaridine interfered with the digestive system of trophozoites in erythrocytic *P. falciparum* cultured *in vitro*, (Wu LJ et al. 1988), and of late trophozoites and schizonts *in vivo* following pyronaridine treatment of primates infected with *P. falciparum* (Kawai S et al. 1996). Subsequent *in*

	vitro studies have reported that pyronaridine inhibited production of and formed complexes with β-hematin to enhance hematin-induced human blood cell lysis (Dorn A et al. 1998; Auparakkitanon Set al. 2006) Pyronaridine has also been shown to inhibit glutathione-dependent haem degradation (Auparakkitanon Set al. 2006; Famin O et al. 1999). A full description of pyronaridine characteristics and activity is reported (Croft S et al. 2012). Artesunate Mode of Action Artemisinin and its derivatives have a rapid onset of action showing activity against ring stage parasites and early trophozoites. Artemisinin is only active on blood stage parasites. However, it does act on gametocyte development resulting in reduced transmission in areas where artemisinin compounds are extensively used. Artemisinin derivatives are selectively toxic to malaria parasites and *P. falciparum*-infected red cells accumulate [^{3}H]-dihydroartemisinin (Gu HM et al. 1984) and [^{14}C]-artemisinin (Meshnick SR et al. 1991) to a much higher intracellular concentration than uninfected red cells. It has been reported that artemisinin derivatives affect parasites differently from other antioxidant drugs. Evidence suggests that the antimalarial endoperoxides have a two-step mode of action. In the first step artemisinin compounds are activated by haem (released during the blood stage of the parasite where haemoglobin is digested) or Fe^{2+} to produce free radicals and alkylating intermediates (Meshnick SR et al. 1993; Kamchonwongpaisan S et al. 1996). This is followed by a second step in which these reactive species react with and damage specific membrane associated proteins (Meshnick SR et al. 1991: Meshnick SR et al. 1994) in erythrocytes. Evidence for an alternative mechanism of action indicates that the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) is a key target for the activity of artemisinin. The inhibitory constants against PfATP6 for artemisinin and its derivates (including DHA, artesunate and artemether) strongly correlated to their ability to kill parasites *in vitro* (Eckstein-Ludwig U et al. 2003).
	Important information about its composition Not applicable
	Module 1.3.1
	Current: 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.

<table>
<tr><td></td><td>Pyramax Granules for oral suspension are indicated in the treatment of acute, uncomplicated malaria infection caused by Plasmodium falciparum or by Plasmodium vivax in children and infants weighing 5 kg to under 20 kg.

Consideration should be given to official guidance on the appropriate use of antimalarial agents.</td></tr>
<tr><td></td><td>Proposed (if applicable): No change.</td></tr>
<tr><td></td><td>
<table>
<tr><th>Body weight</th><th>Number of Tablets</th><th>Regimen</th></tr>
<tr><td>20 - <24 kg</td><td>1 tablet</td><td>Daily for 3 days</td></tr>
<tr><td>24 - <45 kg</td><td>2 tablets</td><td>Daily for 3 days</td></tr>
<tr><td>45 - <65 kg</td><td>3 tablets</td><td>Daily for 3 days</td></tr>
<tr><td>≥65 kg</td><td>4 tablets</td><td>Daily for 3 days</td></tr>
</table>
PYRAMAX should be administered by a physician or by a health care professional under the supervision of a physician.

PYRAMAX should be administered by mouth independent of food intake with water once a day for three days.

If the first dose is vomited within 30 minutes of administration, a second dose should be given.

The tablet should be given whole and not crushed.
<table>
<tr><th>Body weight</th><th>Number of granules sachets</th><th>Regimen</th></tr>
<tr><td>5 - <8 kg</td><td>1 sachet</td><td>Daily for 3 days</td></tr>
<tr><td>8 - <15kg</td><td>2 sachets</td><td>Daily for 3 days</td></tr>
<tr><td>15 - <20 kg</td><td>3 sachets</td><td>Daily for 3 days</td></tr>
</table>
PYRAMAX Granules for oral suspension should be taken orally as a single daily dose for three consecutive days.
</td></tr>
<tr><td></td><td>Proposed (if applicable): No change.</td></tr>
<tr><td>Pharmaceutical form(s) and strengths

Tablets</td><td>Current:

Film coated tablets:

Round, biconvex, orange coloured tablets.

Each tablet is engraved with "PA" on one side.</td></tr>
</table>

Granules	Granules for oral suspension: Orange coloured granules
	Proposed: No change.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Indication:

Uncomplicated malaria caused by *Plasmodium falciparum (P. falciparum)* and *Plasmodium vivax* (*P. vivax).*

SI.2 Incidence:

Global efforts have led to significant progress in the prevention, diagnosis, and management of malaria. However, treatment of malarial infections in the face of emerging drug resistance amongst *Plasmodium s*pp. continues to pose clinical challenges. Widespread resistant strains of *P. falciparum* have rendered previous treatments such as chloroquine, amodiaquine, sulfadoxine and pyrimethamine ineffective, driving the need for new artemisinin-based combination therapies (ACTs). Additionally, the spread of chloroquine-resistant *P. vivax* underscores the need for the evaluation of alternative therapies for the treatment of the blood stage of *P. vivax*. Consequently, new drugs are needed to avoid a global malaria crisis. Mixed infections with *P. falciparum* and *P. vivax* occur in some geographic locations and drugs that clear both species from the circulation are needed. Treatment of malaria with monotherapy is associated with the development of resistance and combinations of anti-malarial drugs with different mechanisms of action are recommended by the World Health Organization (WHO) (WHO, 2015).

Malaria remains a significant global health priority and was estimated to have caused approximately 247 million new cases and 619,000 deaths in 2021 (WHO, 2023). More than 96% of the estimated deaths due to malaria occurred in sub-Saharan Africa, and most (80%) were in children under 5 years of age. *P. falciparum* is the most pathogenic malaria species and is most commonly associated with severe illness and death. More than 90% of malaria-related deaths that occurred in 2018 were caused by *P. falciparum. P. vivax* dominates in South-East Asia, the Americas and Eastern Mediterranean regions (WHO, 2019). *P. vivax* forms persistent hypnozoite parasite stages in the liver that can result in malaria relapses of infection weeks to years after the primary infection.

ACTs are used as first-line treatment for *P. falciparum* malaria in most endemic countries (WHO, 2006; WHO, 2019). Resistance to commonly used ACTs is increasing in South-East Asia and potential spread to African countries is a major concern, as is evidence of the de novo emergence of genes conveying artemisinin resistance in Rwanda. Additionally, the spread of chloroquine-resistant *P. vivax* underscores the need for the evaluation of alternative therapies for the treatment of the blood stage of *P. vivax.* Consequently, new ACTs are needed to maintain the availability of effective treatment options for malaria. Mixed infections with *P. falciparum and P. vivax* and further plasmodium species occur in some geographic locations and drugs that clear both species from the circulation are needed.

Malaria is recognised as a huge public health need. Globally, there were an estimated 247 million malaria cases in 2021 in 84 malaria endemic countries (including the territory of French Guiana), an increase from 245 million in 2020, with most of this increase coming from countries in the WHO African Region. In 2015, the baseline year of the Global technical strategy for malaria 2016–2030 (GTS), there were an estimated 230 million malaria cases. Malaria case incidence (i.e. cases per 1000 population at risk) reduced from 82 in 2000 to 57 in 2019, before increasing to 59 in 2020. There was no change in case incidence between 2020 and 2021. The increase in 2020 was associated with disruption to services during the COVID-19 pandemic.

From the WHO 2022 World Malaria Report, more than 96% of the estimated deaths due to malaria occurred in sub-Saharan Africa, and most (80%) were in children under 5 years of age. *P. falciparum* is the most pathogenic malaria species and is most commonly associated with severe illness and death. More than 90% of malaria-related deaths that occurred in 2018 were caused by *P. falciparum. P. vivax* dominates in South-East Asia, the Americas and Eastern Mediterranean regions (WHO, 2019).

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

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

Common co-morbidities found within the African population include malnourishment, low haemoglobin levels, HIV infection and tuberculosis. A significant, but often overlooked, aspect of malaria is the morbidity impact. Many children who survive an episode of severe malaria may suffer from learning impairments or brain damage. Pregnant women and their unborn children are also particularly vulnerable to malaria, which is a major cause of perinatal mortality, low birth weight and maternal anaemia.

Plasmodium vivax (*P. vivax*) represents a major health problem throughout the tropics. Outside of Africa, it accounts for over 50% of malaria cases, with an estimated number of annual clinical cases ranging from 70 million to 390 million notably in Southeast Asia, India and Central and South America, and has a particularly strong impact on the archipelago of Indonesia as well as in Papua New Guinea. In addition, it is estimated that 10-20% of the *P. vivax* cases occur in Eastern and Southern Africa, while *P. vivax* cases are extremely rare in the countries of sub-Saharan West Africa. This is apparently due to the high prevalence of the Duffy negative trait in West Africans, a phenotype that lacks the receptor for invasion of the human red blood cell (RBC) by *P. vivax* merozoites. Furthermore, in recent years the re-emergence of *P. vivax* has become a major problem in malaria-endemic areas, such as Korea or China, where the disease had been eradicated many years ago. The *P. vivax* infection is responsible for an important morbidity in all age groups. *P. vivax* forms persistent hypnozoite parasite stages in the liver that can result in multiple relapses of infection weeks to months after the primary infection. Thus, a single infection causes repeated bouts of illness that significantly impact subjects' health and ability to carry on activities of daily living. In the majority of cases, *P. vivax* malaria is benign and vital organ dysfunction is very rare. Nevertheless, evidence now also points to this supposedly benign parasite causing a spectrum of severe, life-threatening syndromes and reports of cases of severe *P. vivax* malaria have been published and acute respiratory distress syndrome seems to be one of the more common complications.

The percentage of total malaria deaths among children aged under 5 years declined over the past 20 years, from 87.3% in 2000 to 76.8% in 2015, but since then it has remained unchanged. In 2021, 29 of the 84 countries that were malaria endemic accounted for about 96% of malaria cases and deaths globally. Four countries accounted for almost half of all cases: Nigeria (26.6%), the

Democratic Republic of Congo (12.3%), Uganda (5.1%) and Mozambique (4.1%). Also, four countries accounted for just over half of all malaria deaths globally: Nigeria (31.3%), the Democratic Republic of the Congo (12.6%), Tanzania (4.1%) and the Niger (3.9%). Nigeria accounted for 38.4% of global malaria deaths in children aged under 5 years.

Malaria infection and disease may occur at a similarly low frequency at any age, as little immunity develops. Where the transmission of malaria is stable, i.e. where populations are continuously exposed fairly constantly to a high frequency of malarial inoculation (entomological inoculation rate, > 10/year), partial immunity to clinical disease and a reduced risk of developing severe malaria are acquired in early childhood. The pattern of acquired immunity is similar across the sub-Sahel region, where malaria transmission is intense only during the 3- or 4-month rainy season and relatively low at other times. In both these situations, clinical disease is confined mainly to young children, who may develop high parasite densities that can progress very rapidly to severe malaria.

For *P. falciparum* malaria, artemisinin-based combination therapy (ACT) is generally recommended by the World Health Organization (WHO). Parasite burden and fever are rapidly reduced with ACT and efficacy remains high in most regions. Artemisinin tolerance – observed as extended parasite clearance times with ACT treatment – emerged among *P. falciparum* from the Cambodia–Thailand border areas with some evidence of resistance spreading at the Thailand–Myanmar border. In a study reported in New England Journal of Medicine in September 2021 on a longitudinal study of responses to intravenous artesunate in 240 malaria patients in northern Uganda 6% of patients with increased parasite clearance half-life (>5 hours) and mutations in the *Kelch13* gene demonstrating the independent emergence and local spread of clinically artemisinin-resistant *P. falciparum* in Africa. WHO in 2022 state that the emergence of artemisinin partial resistance in Africa necessitates a response aiming to ensure that efficacious treatments remain available.

For *P. vivax*, the WHO recommends ACT in areas where chloroquine resistance has emerged; most notably Indonesia, though there are also reports from further east in the Malay Archipelago to Papua New Guinea and Vietnam as well as from South America and Oceania. Using ACTs in areas co-endemic for *P. falciparum* and *P. vivax* has also been suggested as a strategy to overcome difficulties in differential diagnosis and in cases of mixed infection.

SI.3 Prevalence:

In 2022, the WHO African Region accounted for about 93.6% of cases and 95.4% of deaths globally; 78.1% of all deaths in this region were among children aged under 5 years in 2022, compared with 90.7% in 2000. Between 2019 and 2020, estimated malaria cases increased from 218 million to 230 million, and deaths from 552 000 to 604 000 in this region.

Between 2020 and 2022, there was almost no change in the estimated number of cases in the region, while deaths decreased to 580,000. However, between 2019 and 2022, there were substantial increases in estimated case numbers in Nigeria (5.3 million), Ethiopia (2.4 million), Madagascar (1.5 million), Uganda (1.3 million), the United Republic of Tanzania (1.3 million), Mali (1.1 million) and Mozambique (1 million). Over the same period, Rwanda saw a decrease of more than 3.8 million cases.

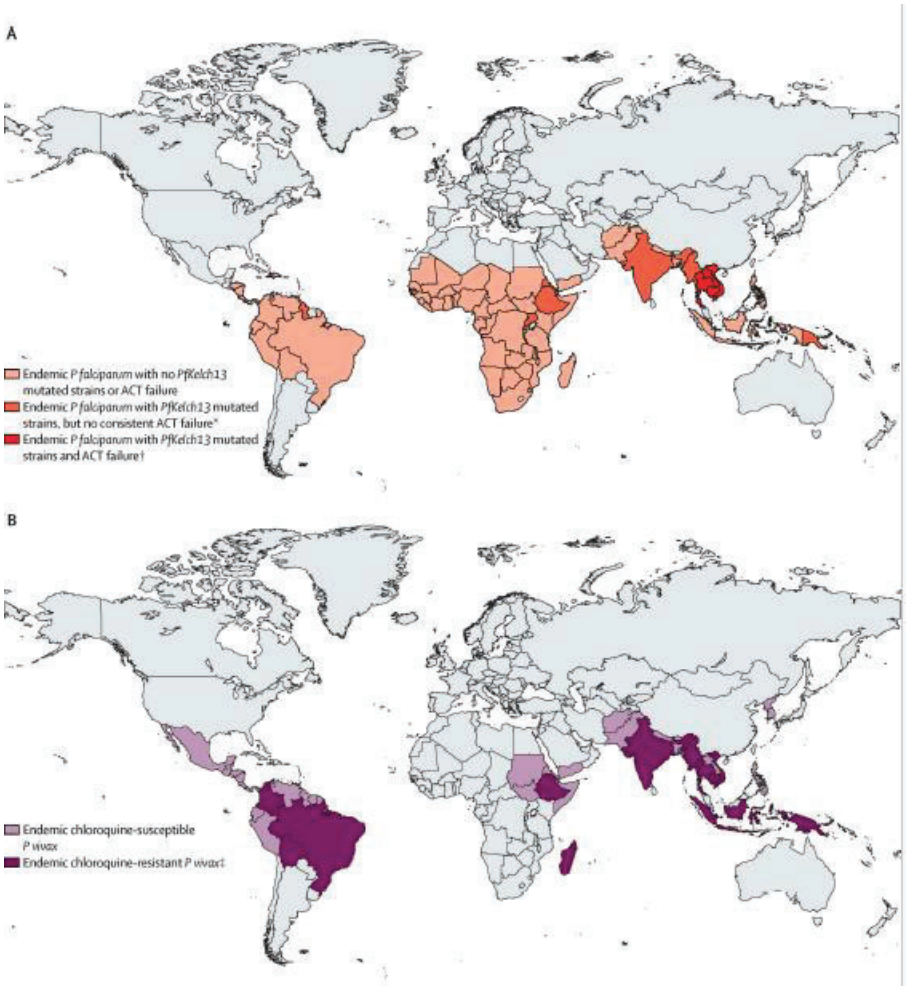
Malaria case incidence decreased from 369.3 per 1,000 population at risk in 2000 to 225.6 in 2019; it then increased to 231.5 per 1,000 population at risk in 2020 but declined to 222.6 in 2022. Between 2021 and 2022, the increasing trend in estimated cases (despite the decline in incidence) was the result of a population at risk that is rapidly increasing, having nearly doubled in sub-Saharan Africa since the turn of the century. Between 2000 and 2019, the malaria mortality rate decreased by 60%,

from 142.6 to 57.1 per 100,000 population at risk. In 2020, the mortality rate increased to 60.9 per 100,000 population before decreasing to 55.5 in 2022.

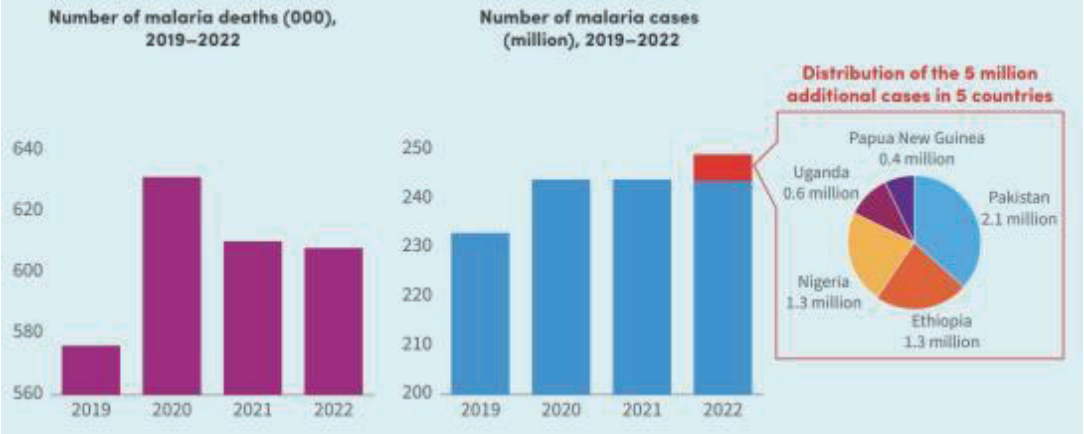
Since 2015, the rate of progress in both cases and deaths has stalled in several countries with moderate or high transmission; the situation was made worse, especially in sub-Saharan Africa, by disruptions during the COVID-19 pandemic and other humanitarian emergencies.

The WHO South-East Asia Region had nine malaria endemic countries in 2022, accounting for 5.2 million cases and contributing to 2% of the burden of malaria cases globally. In 2022, India accounted for about 65.7% of all malaria cases in the region. Almost 46% of all cases in the region were due to *P. vivax*.

Global distribution of malaria cases for *P. falciparum* (A) and P. vivax (B) (from Poespoprodjo, Lancet,2023): Map of *Plasmodium falciparum* (A) and *Plasmodium vivax* (B) endemicity and antimalarial drug resistance as at Jan 31, 2023



SI.4 Demographics of the population in the authorised indication



In Africa approximately 40% of cases are in children <5 years of age; in Southeast Asia the number is closer to 15%. Over three quarters of global malaria deaths occur in children under 5 years old (WHO, 2023), making it a priority to prevent and treat malaria amongst this vulnerable population. Beyond the immediate threat to life, malaria in children can have enduring consequences, affecting cognitive development, impairing educational progress, and undermining overall health and well-being (Oshagbemi OA, 2023). In sub-Saharan Africa, school-aged children, 6 to 15 years old carry the highest burden of malaria, with around 200 million children at risk.

The approximate mean ages in the Phase II and Phase III children-only trials performed for PYRAMAX was 5.5 years and 5 years respectively.

In the Phase IIIb/IV longitudinal study SP-C-013-11 the mean ages of children who received PYRAMAX was 4 years (range < 1 year and 10 years). There was an integrated safety analysis (ISS) performed consisting of all patients who received granules for treatment of their first episode of malaria from studies SP-C-003-05, SP-C-007-07 and the granules sub-group analysis of the sub-study of SP-C-013-11. The 667 patients in this ISS had a mean age of 4.1 years and ranging from < 1 year and 10 years.

The completed phase IIIb/IV cohort study SP-C-021-15 in central and western Africa in adults and children presenting with uncomplicated malaria, a total of 7114 patients were recruited and treated with PYRAMAX for at least one course of treatment. 7154 patients were included in the safety set. 5454/7154 (76.2%) of patients were <18 years at entry to the study. A further breakdown showed 134 patients were <1 year, 1711 patients were 1-<5 years and 3609 patients were 5-<18 years.

A new meta-analysis is now reported (Ramharter, 2024), co-authored by the SOH, which consolidates the clinical data for PYRAMAX paediatric granules in children from three randomized clinical trials and a real-world study (CANTAM). An integrated safety analysis was performed and reported the individual patient data from three randomized clinical trials which included patients with microscopically confirmed *P. falciparum*, body weight≥5 kg to 20 kg who received PYRAMAX. The aim of the analysis was to review the safety and efficacy of PYRAMAX granules for the treatment of children with uncomplicated *P. falciparum* malaria across the core clinical development programme as well as findings from the large post-approval 'real-world' study. The baseline characteristics of the paediatric safety population showed that the majority patients were aged 3 to 5 years, with 3.0% of (20/667) patients in the PYRAMAX group. In this analysis, the mean age was 4.1 years (SD) [range] (2.0) [0–10].

SI.5 Sex differences

Few countries record the sex of reported cases. In 7 Asian countries that did, between 52% and 71% of reported cases were male. The higher incidence in males compared with females in Cambodia, Malaysia and Thailand probably reflects the occupational exposure in parts of these countries, although gender differences in treatment-seeking behaviour might also be a contributing factor (World Malaria Report, WHO 2005).

In the PYRAMAX pre-authorisation clinical trial programme the distribution of Asian male to female demonstrated a higher male incidence with on average 75% being male and 25% female.

Comparable published data for Africa are difficult to find. However, in the PYRAMAX pre-authorisation clinical study programme the distribution between males and females was close to 50:50 (including the paediatric-only study SP-C-007-07). The proportion of males to females receiving PYRAMAX granules in the longitudinal study (SP-C-013-11) was 55% female and 45% male and in the integrated analysis (ISS) was 53.5% female to 46.5% male.

In the PYRAMAX cohort study (SP-C-021-15) to which 7114 patients were enrolled, in terms of adverse event reporting, patients were counted once if they only presented with normal or abnormal LFTs but would be counted more than once if they appeared in more than one LFT category. As a result, the safety population consisted of 7154 patients. There was an almost equal distribution of male and female patients in the safety population overall (n=3569 [49.9%] male; n=3585 [50.1%] female), and this was also reflected across all the age group subcategories.

In the integrated paediatric meta-analysis of the 667 children, the distribution is similar with 46.5% male and 53.5% female.

SI.6 The main existing treatment options:

The treatment of malaria depends on the severity of the disease with uncomplicated malaria treated with oral medications. The most effective strategy for *P. falciparum* infection is the use of artemisinins in combination with other antimalarials (known as artemisinin-combination therapy, or ACT), which reduces the ability of the parasite to develop resistance to any single drug component. These additional antimalarials include amodiaquine, lumefantrine, mefloquine or sulfadoxine-pyrimethamine. Another recommended combination is dihydroartemisinin-piperaquine.

ACT is about 95% effective when used to treat uncomplicated malaria. Treatment of *P. vivax* requires both treatment of blood stages (with chloroquine or ACT) as well as clearance of liver forms with primaquine.

Paediatric formulations of most of the current commercially available ACTs have been developed predominantly as fixed dose regimen dispersible tablets such as artemether-lumefantrine which has EU regulatory approval or DHA-piperaquine which is under development as a paediatric formulation.

The paediatric formulation of PYRAMAX is specifically formulated for children <20 kg in weight and is considered to be important in global health terms.

In the treatment of uncomplicated malaria in pregnant women, WHO have recently updated their guidance in relation to the treatment in pregnancy with ACTs. The redirection by WHO is predominantly based on a seminal paper authored by Saito et. al, 2023 entitled "Pregnancy outcomes after first-trimester treatment with artemisinin derivatives versus non-artemisinin antimalarials: a systematic review and individual patient data meta-analysis". The findings from the systematic review and meta-analysis were reflected in the WHO Guidelines for Malaria (16 October 2023). Until late 2022 WHO treatment guidelines recommended 7 days of quinine for treating uncomplicated *P.*

falciparum malaria in the first trimester of pregnancy, despite its poor tolerability, adherence, and effectiveness. In 2017, a systematic literature review and meta-analysis assessed the safety of artemisinin derivatives in the first trimester of human pregnancies, showing no difference in the risk of miscarriage, stillbirth, and congenital anomalies between artemisinin-exposed and quinine-exposed pregnancies. In 2021, WHO sought to gather the evidence on the safety of antimalarials in the first trimester of pregnancy to establish whether ACTs could be reconsidered for the treatment of malaria in the first trimester. Resulting from the examination of a large dataset of cases for first trimester pregnancies WHO has generated a new recommendation based on a review of all updated evidence to date on the risks and benefits of using any ACT compared to quinine for the treatment of uncomplicated *P. falciparum* malaria in the first trimester of pregnancy. The WHO guidance with regards to 2nd and 3rd trimesters pregnancy is that the artemisinin derivatives should be used to treat uncomplicated *P. falciparum* malaria in the second and third trimesters of pregnancy as there have been no adverse effects on the mother or foetus in large numbers of documented pregnancies. ACTs, particularly artemether-lumefantrine, have thus been the recommended first-line treatment in the second and third trimesters of pregnancy since 2006 and the extension of use to other ACTs has been made by WHO in the 2023 Guidance.

Resistance has developed to several antimalarial drugs; for example, chloroquine-resistant *P. falciparum* has spread to most malarial areas. Emerging resistance to artemisinin has become a problem in some parts of Southeast Asia while mutations in the *Kelch13* gene demonstrating the independent emergence and local spread of clinically artemisinin-resistant *P. falciparum* have been reported in Africa.

Treatment options which allow for re-treatment in a given individual are clearly advantageous from a patient perspective, allowing for a well-tolerated drug to be administered on more than one occasion, as well as from a public health perspective in terms of health policy and treatment guidelines for antimalarials, drug access, stockage and distribution.

SI.7 Natural history of the indicated condition in the untreated population, including mortality and morbidity:

As reported in the 2023 WHO World Malaria Report, the large disruptions to malaria services during the COVID-19 pandemic drove up malaria incidence and mortality rates at a time when progress against the disease had already stalled. Malaria-endemic countries, with the support of global partners, have since managed to stabilize those rates, but at a very high level. In terms of both malaria cases and deaths, the world is worse off now than before the pandemic (WHO, 2023). Five countries bore the brunt of these increases, hindered by multiple challenges including climate change.

The number of global malaria cases in 2022 was significantly higher than before the pandemic in 2019. From 2000 to 2019, the number of global malaria cases fell from 243 million to 233 million. There were an additional 11 million cases in 2020, no change in 2021, and then an increase of 5 million cases in 2022, to a total of about 249 million cases. The number of global malaria deaths in 2022 was higher than in 2019: since 2000, malaria deaths declined steadily from 864,000 to 576 000 in 2019. With the onset of the pandemic, the number of deaths increased by 55,000 in 2020, to 631,000. Marginal decreases in the following two years resulted in an estimated 608,000 deaths in 2022 being 32 000 more deaths than before the pandemic.

The global malaria case incidence remains slightly higher than in 2019. The case incidence rate (number of cases per 1000 population at risk) declined from 81 in 2000 to 56.8 per population at risk in 2019. By 2020, the rate had climbed to 58.7. A small decrease in 2021 was followed by a small increase in 2022, which ended with a rate of 58.4 per population at risk. The global malaria

mortality rate remains slightly higher than in 2019. The malaria mortality rate (number of deaths per 100,000 population at risk) halved between 2000 and 2019, from 28.8 to 14.1. In 2020, this rate increased to 15.2 before decreasing slightly to end 2022 at 14.3.

The 5 million additional cases observed between 2021 and 2022 were mainly concentrated across five countries with Pakistan with the largest rise (2.1 million more cases), followed by Ethiopia and Nigeria (+ 1.3 million each), Uganda (+ 597 000), and Papua New Guinea (+ 423 000). In Pakistan, case incidence jumped five-fold, from 2.2 to 11.5 cases per 1000 population at risk. Meanwhile, case incidence increased by 32% in Ethiopia (from 46.3 to 60.9); by 32% in Papua New Guinea (from 124.3 to 163.7); and by 2% in Uganda (from 262.9 to 267.8). In Nigeria, the increase in cases was attributable to population growth as incidence remained unchanged.

In terms of achievement of WHO Global Technical Strategy (GTS) goals, in 2022, the global malaria case incidence was 58.4 against a target of 26.2 cases per 1,000 population at risk. Progress towards the 2025 milestone for case incidence is 55% off track and, if this trajectory persists, the corresponding 2030 GTS target will be missed by 89%. The global malaria mortality rate in 2022 was 14.3 against a target of 6.6 deaths per 100,000 population at risk, off the mark by 53%. Without an acceleration in the pace of progress, the 2030 outlook indicates a potential 88% shortfall.

As malaria continues to threaten global public health, especially in Central Sub-Saharan Africa and Western Sub-Saharan Africa with children 1–4 years old continuing to bear the most significant burden of malaria. A paper by Shi et al. (2023) reports trends of the global, regional and national incidence, mortality, and disability-adjusted life years of malaria (1990–2019) and an analysis of the global burden of disease study 2019. This paper reports that while the burden of malaria decreased globally between 1990 and 2019 there were 2313.57×105 incident cases and 6.43×105 deaths in 2019, contributing to 464.38×105 disability-adjusted life years (DALYs). The largest incident cases were observed in Western Sub-Saharan Africa [1151.72 (95% UI: 890.01–1527.17)] ×105 in 2019. The only region where deaths increased between 1990 and 2019 was Western Sub-Saharan Africa. Age standardised rates of malaria are distributed heterogeneously in different regions. The highest age-standardized incidence rates were observed in Central Sub-Saharan Africa [21,557.65 (95% UI: 16,639.4–27,491.48)] in 2019. Compared to other age cohorts, the age-standardized incidence rates, age-standardized mortality rates and age-standardized DALY rates for children aged between 1 to 4 years were found to be higher. Worst-affected regions by malaria infection were the low-middle socio-demographic index (SDI) region and low SDI region.

Children in sub-Saharan Africa remain the most vulnerable to malaria and malaria mortality. The disease burden and distribution of *P. falciparum* malaria among children with age categories (0 to < 2 years, 2 to < 6 years, 6 to < 12 years, ≥ 12 years): being 15.4% for ages 0 to < 2 years, 30.5% for 2 to < 6 years, 17.6% for 6 to < 12 years, and 36.5% for ≥ 12 years (Oshagbemi et al. 2023).

In 2018, there were an estimated 405,000 deaths from malaria globally, compared with 416,000 estimated deaths in 2017, and 585,000 in 2010. The WHO African Region had the largest absolute reduction in malaria deaths, from 533 000 in 2010 to 380,000 in 2018. Despite these gains, the malaria mortality reduction rate has also slowed since 2016. In South-east Asia, there were an estimate of 12,000 deaths in 2018 representing a significant reduction as the estimated number of deaths was 25,000 in 2016 and 20,000 in 2017. In Western Pacific region the estimated number of deaths remains stable with 3,600 in 2018 (WHO World Malaria Report, 2019 Appendix 3F). A further downward trend was reported in the World Malaria Report 2019, which reports that an estimated 228 million cases led to an estimated 405,000 malaria deaths worldwide in 2018 (WHO report 2019). Of the estimated deaths, the WHO African Region accounted for 94% of all malaria deaths in 2018 and in children under 5 years of age (67%). This trend has reversed and as reported earlier the number of global malaria deaths in 2022 was higher than in 2019 (WHO, 2023). With the onset of

the pandemic, the number of deaths increased by 55,000 in 2020, to 631,000 with marginal decreases in the following two years resulted in an estimated 608,000 deaths in 2022 being 32,000 more deaths than before the pandemic.

Malaria in Pregnancy

As reported by Gore-Langton et al. (2020), globally in 2020, 120.4 million pregnancies were at risk of *P. falciparum*, two-thirds (81.0 million, 67.3%) were in areas of stable transmission while 85.2 million pregnancies were at risk of *P. vivax*. An estimated 64.6 million pregnancies were in areas with both *P. falciparum* and *P. vivax* transmission. The total number of pregnancies at risk of *P. falciparum* increased to 52.4 million in 2020. The adverse effects of P*. falciparum* are thought largely due to the sequestration of the parasite within the placenta and are particularly seen in women who have not been exposed to *P. falciparum* in any previous pregnancy.

Malaria in pregnancy affects more than 25 million pregnant women every year, both in high and low malaria-endemic areas (WHO 2020). Malaria in pregnancy is associated with a 33% increase in pregnancy loss, and this increase can be as high as 60% in the first trimester. Malaria infection in the first trimester impairs placental vasculogenesis and angiogenesis as well as placental villous and vascular development, leading to gestational hypertension, maternal anaemia, low birth weight, foetal growth restriction, preterm birth, and pregnancy loss. Up to 200,000 infant deaths and 10,000 maternal deaths occur annually due to malaria in pregnancy (Desai et al., 2007). Maternal anaemia due to malaria is an independent risk factor for low birth weight and other impact factors on mother and baby. Malaria has been estimated to cause 24% of all low-birth-weight babies (WHO 2020). Low infant birth weight is the greatest single risk factor for death in the first month of life. In areas where malaria is endemic, 20-40% of all babies born may have a low birth weight.

The risk of malaria infection is said to be highest in the first and second trimesters of pregnancy. Pregnant women constitute the main adult risk group for malaria and 80% of deaths due to malaria in Africa occur in pregnant women and children below the age of 5 years. Malaria is more common in pregnancy compared to the general population and malaria tends to be more atypical in presentation. This could be due to the hormonal, immunological and haematological changes of pregnancy with parasitaemia tending to be 10 times higher and as a result, all the complications of *P. falciparum* malaria are more common in pregnancy compared to the non-pregnant population. *P. falciparum* malaria in pregnancy is reported as more severe, with the mortality is also double compared to the non-pregnant population.

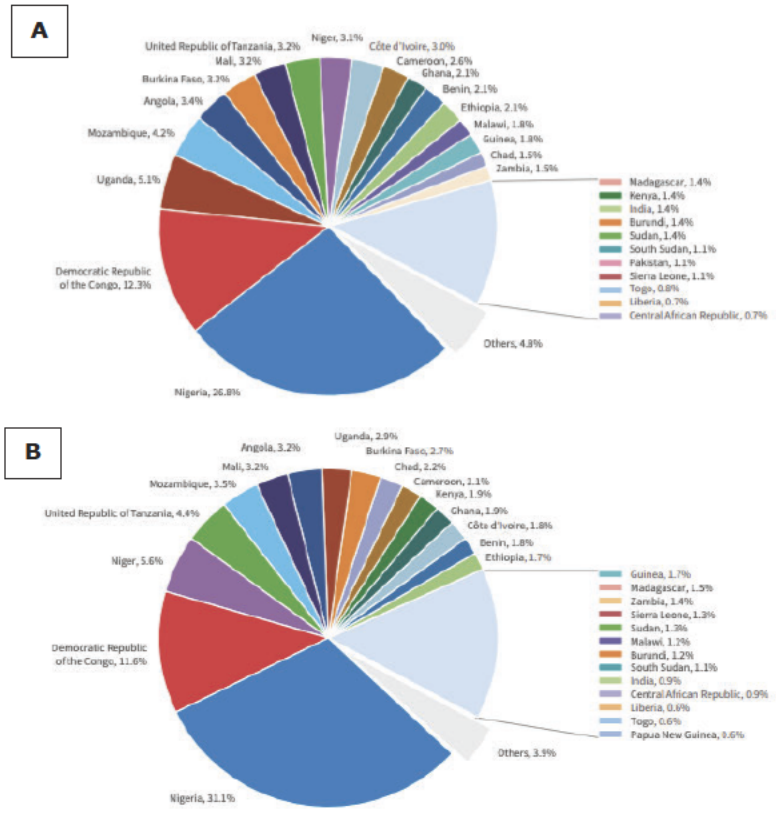
WHO provides clear direction that ACTs should be used to treat uncomplicated malaria preferentially over the previous standard of care, quinine, in second and third trimester of pregnancy. In first trimester, WHO has issued revised guidance (2023) weighing the risk–benefit ratio, safety risks from antimalarial treatment against the adverse effects of malaria in the first trimester. The updated individual patient data review by WHO showed that first-trimester treatment with artemether-lumefantrine was associated with significantly fewer adverse pregnancy outcomes than first-trimester treatment with quinine. Treatment with artemether-lumefantrine in the first trimester was associated with a statistically significant lower risk (42%) of adverse pregnancy outcomes compared to treatment with oral quinine. The numbers of exposures to the other ACTs were considered by WHO to be low, although prospective research projects are underway to document the findings in first, second and third trimesters of pregnancy with other ACTs including PYRAMAX.

Table SI.1. Global estimated malaria cases and deaths *P. falciparum* and *P. vivax* 2000-2022, WHO

Global estimated malaria cases and deaths, 2000–2022[a] *Source: WHO estimates.*

Year	Number of cases (000)				Number of deaths		
	Point	Lower bound	Upper bound	% *P. vivax*	Point	Lower bound	Upper bound
2000	**243 000**	227 000	263 000	8.3%	**864 000**	835 000	905 000
2001	**248 000**	230 000	271 000	8.3%	**873 000**	841 000	918 000
2002	**245 000**	227 000	267 000	7.7%	**841 000**	811 000	885 000
2003	**249 000**	232 000	271 000	8.0%	**813 000**	783 000	856 000
2004	**250 000**	232 000	277 000	7.9%	**808 000**	774 000	866 000
2005	**249 000**	232 000	273 000	8.0%	**770 000**	738 000	819 000
2006	**244 000**	226 000	268 000	6.9%	**776 000**	745 000	826 000
2007	**240 000**	223 000	262 000	6.6%	**754 000**	723 000	796 000
2008	**239 000**	223 000	259 000	6.4%	**716 000**	686 000	757 000
2009	**245 000**	227 000	267 000	6.4%	**726 000**	692 000	775 000
2010	**247 000**	229 000	272 000	6.6%	**703 000**	668 000	755 000
2011	**241 000**	225 000	263 000	7.0%	**665 000**	633 000	707 000
2012	**237 000**	221 000	257 000	7.0%	**619 000**	590 000	660 000
2013	**232 000**	215 000	251 000	6.0%	**591 000**	560 000	633 000
2014	**230 000**	209 000	253 000	5.5%	**588 000**	551 000	643 000
2015	**231 000**	211 000	254 000	4.9%	**586 000**	548 000	645 000
2016	**232 000**	214 000	253 000	4.6%	**582 000**	546 000	645 000
2017	**237 000**	219 000	258 000	3.7%	**580 000**	545 000	644 000
2018	**232 000**	215 000	253 000	3.0%	**581 000**	545 000	656 000
2019	**233 000**	213 000	255 000	2.7%	**576 000**	537 000	660 000
2020	**244 000**	221 000	271 000	1.9%	**631 000**	587 000	747 000
2021	**244 000**	220 000	272 000	2.1%	**610 000**	568 000	726 000
2022	**249 000**	225 000	278 000	2.8%	**608 000**	566 000	738 000

Figure 1 Percentage of total malaria deaths based on country distribution for over 5 years (A) and under 5 years (B)



SI.8 Important co-morbidities found in the target population:

Common co-morbidities include malnourishment, low haemoglobin levels, HIV infection, tuberculosis (TB) and pregnancy.

Malaria and HIV	The prevalence of HIV within sub-Saharan Africa is estimated at 30 million sufferers. Data suggest an increased frequency of clinical malaria and parasitaemia with increasing immunosuppression (Whitworth J et al. 2000). *P. falciparum* has been shown to stimulate HIV-1 replication (Kublin JG et al. 2005) and therefore may cause faster progression of HIV-1. In addition, medication taken for HIV (e.g. co-trimoxazole), may also increase the risk of haematological side effects. Evidence points to the hydroxylamine derivatives of sulphamethoxazole as the reactive metabolites that cause adverse reactions to co-trimoxazole. HIV-positive individuals have a systemic glutathione deficiency, and therefore a reduced capacity to scavenge such metabolites. This process would lead to an increased exposure to toxic intermediates and would explain the high frequency of adverse reactions to co-trimoxazole in these patients. PYRAMAX may alter blood levels of anti-retroviral treatments - as has been demonstrated with ritonavir; probably through P-gp inhibition.
Malaria and tuberculosis	These two infections can co-exist in the same populations and it has been suggested that malarial parasites can decrease their vertebrate host's effective humoral and cellular immune responses. In a review, **Enwere GC et al. (1999)** discussed the possible ways in which this malaria-induced immune impairment could affect the host's response to *Mycobacterium tuberculosis* .
Malaria and pregnancy	WHO provides clear direction that ACTs should be used to treat uncomplicated malaria preferentially over the previous standard of care, quinine, in the second and third trimester of pregnancy. In first trimester, WHO has issued revised guidance (2023) weighing the risk–benefit ratio, safety risks from antimalarial treatment against the adverse effects of untreated malaria in the first trimester. The updated individual patient data review by WHO showed that treatment with artemether-lumefantrine in the first trimester was associated with a statistically significant lower risk (42%) of adverse pregnancy outcomes compared to treatment with oral quinine. The numbers of exposures to the other ACTs were considered by WHO to be low, although prospective research projects are underway to document the findings in first, second and third trimesters of pregnancy with other ACTs including PYRAMAX. As reported above, malaria in pregnancy affects more than 25 million pregnant women every year, both in high and low malaria-endemic areas (WHO 2020). Malaria in pregnancy is associated with a 33% increase in pregnancy loss, and this increase can be as high as 60% in the first trimester. *P. falciparum* malaria in pregnancy being more severe, the mortality is also double (13%) compared to the non-pregnant population (6.5%). Pregnant women constitute the main adult risk group for malaria and 80% of deaths due to malaria in Africa occur in pregnant women and children below the age of 5 years. In Africa, perinatal mortality due to malaria is at about 1,500/day. In areas where malaria is endemic, 20-40% of all babies born may have a low birth weight.

<table>
<tr><td></td><td>Malaria is more common in pregnancy compared to the general population. Immuno-suppression and loss of acquired immunity to malaria could be the causes.

In pregnancy, malaria tends to be more atypical in presentation. This could be due to the hormonal, immunological and haematological changes of pregnancy.

Due to hormonal and immunological changes, the parasitaemia tends to be 10 times higher and, as a result, all the complications of P. falciparum malaria are more common in pregnancy compared to the non-pregnant population.

Management of complications of malaria may be difficult due to the various physiological changes of pregnancy. Careful attention has to be paid towards fluid management, temperature control, etc. Also, decisions regarding induction of labour may be difficult and complex. Foetal loss, intra-uterine growth restriction and premature labour are common.</td></tr>
<tr><td>Malaria and malnourishment</td><td>Children with severe malnutrition (<70% normal weight/height) have a markedly increased risk of mortality. This mortality is often due to infections, of which malaria is a very important one. The pathological changes include immunological deficiency in the humoral and cellular subsystem from protein deficiency and lack of immune mediators. Metabolic disturbances also play a role in impaired intercellular degradation of fatty acids because of impaired carbohydrate deficiency. Table shows the prevalence of protein energy malnutrition in young children in developing countries (Table SI.2) (Müller & Krawinkel M 2005).

Table SI.2 Prevalence of protein-energy malnutrition among children <5 years old in developing countries (1995)

<table>
<tr><th>Region</th><th>Stunting (%)</th><th>Underweight (%)</th><th>Wasting (%)</th></tr>
<tr><td>Africa</td><td>39</td><td>28</td><td>8</td></tr>
<tr><td>Asia</td><td>41</td><td>35</td><td>10</td></tr>
<tr><td>Latin America and Caribbean</td><td>18</td><td>10</td><td>3</td></tr>
<tr><td>Oceania</td><td>31</td><td>23</td><td>5</td></tr>
</table>

Severely malnourished children may have a high parasitaemia while showing few or none of the classic signs of malaria. Fever may be absent. These children are very vulnerable to developing severe malaria disease that can be rapidly fatal (WHO/RBM Consultation 2005).</td></tr>
<tr><td>Malaria and Anaemia</td><td>The prevalence of anaemia varies from territory to territory and also within defined population groups. Therefore, in Africa and Asia the prevalence of anaemia is 40.7% (Africa) and 58% (Asia). However, in pre-school children this rises to 76.7% (Africa) and 82.1% (Asia) with similar values for pregnant and non-pregnant women of approximately 65% (Africa) and 85% (Asia) (WHO Global Database, 2008).

Data from moderate to high malaria burden countries between 2015 and 2018 showed that, among children aged under 5 years positive for malaria, 9% had severe anaemia, 54% had moderate anaemia, 21% had mild anaemia and only 17% had no anaemia. In contrast, among those children who had no malaria,</td></tr>
</table>

	1% had severe anaemia, 31% had moderate anaemia, 28% had mild anaemia and 40% had no anaemia (Malaria World Report 2019). In published series of children admitted to hospital with severe malaria anaemia (including those with other severity manifestations) mortalities range from 2.6 to 10.3%—while mortalities as low as 0.5% have been reported in children with severe anaemia but without any other severity manifestation (White 2018) The attributable risk of anaemia and severe anaemia (< 8 g/dl) as a result of malaria was reported as 5 and 23% respectively in a study of an urban west African population (Klinkenberg E et al. 2006).
Malaria and concomitant liver disease	Hepatitis can be a manifestation of malaria and is a complication in malaria in about 15% of patients however, this would generally be evident from clinical symptoms (Mittal et al 2014; Bhalla et al. 2006). In a report by Obiajuru (Obiajuru et al. 2014) 719 male and female patients, 156 (21.7%) had non - infectious hepatitis, 40 (5.6%) had hepatitis B, 21 (2.9%) had hepatitis C and 404 (56.6%) had malaria parasites. Occupational related prevalence study showed that out of 206 traders, 67 (32.5%) had hepatitis and 148 (71.8%) had malaria. Out of 184 students, 46 (25%) had hepatitis and 92 (50.5%) had malaria. Out of 162 housewives and applicants, 47 (29.01%) had hepatitis, 66 (40.7%) had malaria. Out of 102 public servants, 30 (29.4%) had hepatitis and 60 (58.8%) had malaria. 27 (41.5%) and 38 (58.5%) out of 65 artisans had hepatitis and malaria respectively. Analysis of the data using chi square showed no significance difference ($p > 0.05$) in the prevalence of hepatitis and malaria between the different age groups. In addition, Comparative analysis of the prevalence of hepatitis and malaria between pregnant and non – pregnant women showed that out of 207 pregnant women examined, 50 (24.2%) had non - infectious hepatitis, 15 (7.2%) had hepatitis B, 8 (3.9%) had hepatitis C and 141 (68.1%) had malaria. Amongst non - pregnant women, 32 (17.9%) out of 179 respondents had non - infectious hepatitis, 7 (3.9%) had hepatitis B, 4 (2.2%) had hepatitis C and 95 (53.1%) had malaria. Statistical analysis of the data using chi square showed significant difference ($p < 0.05$) in the prevalence of hepatitis and malaria between pregnant and non – pregnant women.

Part II: Module SII - Non-clinical part of the safety specification

SII.1 Safety pharmacology

SII.1.1 Toxicity

The safety profile of PYRAMAX as the 3:1 combination of pyronaridine tetraphosphate and artesunate, and/or each component studied separately, was assessed in a battery of nonclinical safety pharmacology and *in vitro* and *in vivo* oral-dosed toxicity studies that included:

- Single and repeat-dose studies. The single-dose toxicity studies were performed in rats while the repeat-dose toxicity studies were performed in rats and dogs.
- Reproductive and developmental studies (pyronaridine tetraphosphate and artesunate separately) were performed in rat and rabbit.
- Genotoxicity studies.
- Safety pharmacology studies including cardiovascular, neurobehavioral, motor coordination and respiratory parameters plus effects on analgesia and the gastrointestinal and renal systems.

[redacted]

[redacted]

[redacted]

[redacted]

SII.1.9 Reproductive and Developmental Toxicity

Fertility

Neither pyronaridine tetraphosphate nor artesunate have effects on rat male fertility although abnormal sperm morphology was observed with artesunate in the rat this was only significant at 30 mg/kg however, there was no effect on fertility or pregnancy indices nor any treatment effects on corpora lutea, implantations and live foetuses, foetal death or post implantation losses (KIT/G02014).

The HED of artesunate is similar to that used in the clinical studies, the fact that there appeared to be no effect on fertility would suggest that there should not be an effect in humans. Furthermore, the short treatment and short half-life of artesunate would suggest that any effect on sperm should it occur would be short lived.

Embryotoxicity

The artesunate component of PYRAMAX, in common with other artemisinins is embryolethal. Pyronaridine tetraphosphate causes maternal toxicity to rats and rabbits at high doses but is not teratogenic. Although PYRAMAX, as the combination, has not been tested in reproductive and developmental studies; it would be expected to be embryotoxic.

Reference to preclinical data on embryotoxicity is provided in Section 4.6 and 5.3 in the SmPC.

Lactation

Pyronaridine tetraphosphate distributes from blood into milk in the rat with the ratio of milk to blood being approximately 0.25 to 0.36. The suckling rats therefore receive low levels of pyronaridine tetraphosphate via milk with the ratio of pup to maternal female blood concentration being in the range of 0.051 to 0.071.

It is not known whether artesunate or pyronaridine tetraphosphate are excreted in human milk. In the event of administration of PYRAMAX, to breastfeeding women, alternative infant nutrition methods are recommended as the effects of PYRAMAX, have not been determined.

SII.1.10 Genotoxicity

Pyronaridine was positive in the following *in vitro* genotoxicity assays:

(i) Ames test in *S. typhimurium* TA1537 in the presence and absence of S9 (consistent with the induction of frame shift mutations through direct DNA intercalation).

(ii) Mouse lymphoma L5178Y *tk* mutation assay in the presence and absence of S9 (preponderance of small colony mutants consistent with a clastogenic effect)

(iii) Cytogenetic assay in Chinese hamster CHL cells in the presence and absence of S9 (increase in percentage of chromosome aberrations and polyploid cells).

The positive findings *in vitro* with mammalian cells are consistent with the inhibition of topo-isomerase II enzyme, rather than through direct DNA interaction. (Mechanistic studies have confirmed that pyronaridine is a topo-isomerase II inhibitor)

Pyronaridine was negative in the following *in vivo* assays:

(i) Mouse bone marrow micronucleus test.

(ii) Rat liver in vivo/in vitro Unscheduled DNA Synthesis (UDS) assay

(iii) Rat liver comet assay. In this assay negative results were obtained at liver concentrations up to 4,800 µg/g (mean concentration 3680 µg/g).

Artesunate and its major impurity, Impurity C, were considered to be without genotoxic potential in a series of *in vitro* and *in vivo* assays (artesunate only).

No genotoxicity was detected up to the highest dose tested in the rat Comet study (2000 mg/kg) and the liver concentration at this dose of 3680 µg/g represents an extrapolated safety margin in man of 5068-fold over the mean blood Cmax (0.726 µg/ml pyronaridine in blood on Day 3 of a PYRAMAX treatment cycle) and > 45-fold over extrapolated potential human liver concentrations (the actual safety margin not being known as the highest administered dose did not cause any genotoxicity).

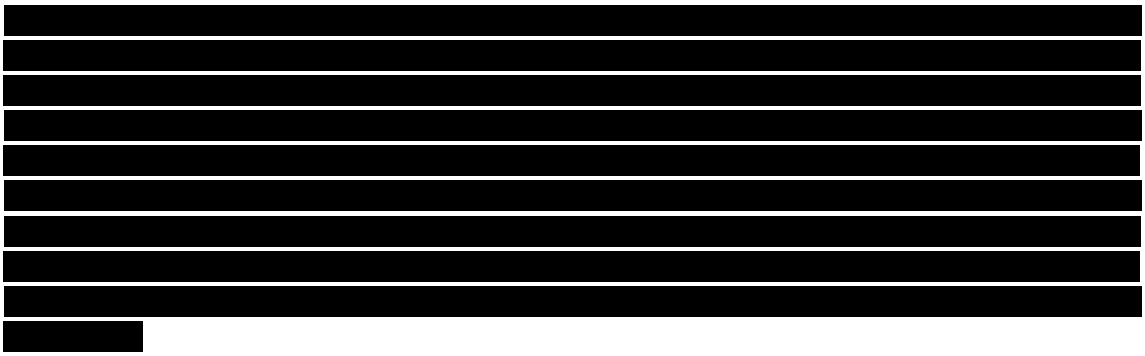
It is considered that the determination of a margin of exposure obtained from this in vivo study designed to detect the biological effects of topoisomerase II inhibition (induction of DNA strand breakage) is more meaningful than the margin of exposure calculation based upon *in vitro* enzyme inhibition studies using a cell-free system. Therefore, given this in vivo large safety margin, PYRAMAX does not appear to be genotoxic *in vivo*.

SII.2 Conclusions from non-clinical data

Preclinical studies have shown that pyronaridine tetraphosphate:artesunate (3:1) is an effective potential therapeutic for malaria and the combination of pyronaridine tetraphosphate and artesunate has been shown to be efficacious.

Artesunate is without genotoxic activity both *in vitro* and *in vivo* and pyronaridine is a genotoxin with activity towards both bacterial and mammalian cells *in vitro* but not *in vivo*. Pyronaridine tetraphosphate:artesunate (3:1), because of the artesunate content, is embryotoxic but not teratogenic.

Notable toxicity arising from repeated dosing of pyronaridine tetraphosphate:artesunate (3:1) in rat and dog was principally associated with accumulation of pyronaridine and concomitant tissue inflammation believed to occur as the body attempts to remove these deposits. Accumulation was associated with visible external and internal yellow discolouration of the animals and the tissue inflammation was associated with increases in white blood cell count, particularly neutrophils and monocytes. Where accumulation was minimal, there was no accompanying inflammatory response in any tissue and, in certain tissues such as eye and bone marrow, accumulation was also not accompanied by inflammatory responses. Whilst changes were seen in a widespread number of organs and tissues following 4-cycles of dosing in animals, in the single cycle study in rat and dog, inflammatory changes were confined to minimal to mild changes in brain (dog only) and liver.



PYRAMAX administration has resulted in reversible, clinically relevant elevations in hepatic biochemistry parameters, particularly ALT and AST, in healthy subjects at a substantially higher rate than in malaria-infected subjects. *In vitro* toxicity analyses conducted with isolated mouse mitochondria, HepRG human cells, rat hepatocytes, and freshly isolated human hepatocytes suggest that pyronaridine may be associated with concentration-dependent hepatocellular damage to hepatocytes; the effect appears likely to be related to glutathione depletion. Malaria patients experience lower exposure to pyronaridine than healthy subjects for equivalent mg/kg dosing. Furthermore, double peaking, likely associated with enterohepatic recirculation, occurs less often among malaria-infected patients than healthy subjects. Enterohepatic recirculation can not only

increase blood exposure to a drug, but also can specifically increase hepatocyte exposure. Importantly, expression of efflux transporters associated with enterohepatic recirculation may be decreased during acute inflammation, an effect which would account for low recirculation during acute malaria. Although the available evidence makes it difficult to ascertain whether metabolites play a role in toxicity, generation of metabolites would also presumably be decreased during acute malaria infection, reducing any toxicity associated with metabolites. Ultimately, the effects of acute inflammation would lead to lower pyronaridine hepatocyte concentrations in infected as compared to healthy subjects, thereby substantially reducing the risk of the toxicity stemming from pyronaridine or its metabolites. The faster rate of absorption in healthy subjects, as indicated by a shorter T_{max}, could also contribute to higher initial blood concentrations of pyronaridine. Given the *in vitro* evidence that pyronaridine exerts effects on hepatocytes in a concentration-dependent manner, and that hepatocyte concentrations of pyronaridine are lower in acute malaria, it follows that the risk of clinically relevant hepatic biochemistry parameter elevations is expected to be much lower in malaria patients then in healthy volunteers.

In the line extension for the use of PYRAMAX to include malaria patients 5 kg to <20 kg in weight, there have been no changes to the drug product or excipients which would justify further non-clinical studies. [redacted] In addition, this is supported by the absence of any specific, additional, safety concern with exposure to PYRAMAX in the younger age group and the number of children that have been treated with single cycles as well as intermittent repeat cycles with the PYRAMAX paediatric formulation in the longitudinal study SP-C-013-11.

List of Safety Concerns from Nonclinical Data:

This includes only those concerns from nonclinical data where which might constitute relevance to human usage as a potential concern:

Safety concerns updated RMP Version 18.1 2025
Important missing information Use in pregnancy and lactation - Embryotoxicity/teratogenicity

Part II: Module SIII - Clinical trial exposure

Total person exposure for population from all Phase II/III completed studies for *P. falciparum* and *P. vivax* indications (person time provided for final duration category and total)								
	SP-C-002-05	SP-C-003-05	SP-C-004-06	SP-C-005-06	SP-C-006-06	SP-C-007-07	SP-C-008-07	Total Phase II/III studies
Duration of exposure	Persons							
Cumulative up to 1 day	3	2	1	11	0	2	0	19
Cumulative up to 2 days	0	0	5	9	1	3	0	18
Cumulative up to 3 days	473	57	842	829	227	350	15	2793

PA: Pyronaridine: artesunate, PP: Pyronaridine tetraphosphate, AS: artesunate

In Study SP-C-009-07, 37 subjects who completed the study per protocol received two oral doses of 720:240 mg pyronaridine tetraphosphate-artesunate with the administration of test and reference formulation in two subsequent periods separated by a wash-out of 43 days. In addition, 5 subjects received only one dose of 720:240 mg pyronaridine tetraphosphate -artesunate (3 received the reference tablet and 2 received the "to be marketed" tablet).

	SP-C-013-11	SP-C-018-13	SP-C-019-14	SP-C-020-15	SP-C-021-15	SP-C-026-18	SP-C-022-17	SP-C-024-17	Total Phase IIIb/IV/TES studies
Duration of exposure	Persons								
Cumulative up to 1 day						102			102
Cumulative up to 2 days						100			100
Cumulative up to 3 days	1407*	60	123	101	7114*	101	176	121	9203

* Includes 1st episode of treatment only – no retreatment is given in less than 28 days and 65 patients who received one episode only as part of a PK subgroup. For details of repeat 3-day treatment episodes see information on SP-C-013-11 (Table SIII.6) and SP-C-21-15

[redacted]

Updated PYRAMAX cumulative safety in trials

The cumulative safety of PYRAMAX has been evaluated in 12,542 subjects from 22 company sponsored completed studies. Of this total population, 12,235 subjects with parasitaemia (clinical malaria and asymptomatic) have received PYRAMAX in clinical trials**.** [redacted]

[redacted]

Table SIII.1. Person Exposure in malaria by age group and gender (Blinded Studies)

	Persons (n)					
	SP-C-005-06		SP-C-006-06		SP-C-008-07	
TOTAL	849		228		15	
Age group (years of age)*						
<1	0		0		0	
1-<5	0		0		0	
5-12	378		14		0	
>12 - <18	191		21		1	
≥18	280		193		14	
Gender	M	F	M	F	M	F
	490	359	172	56	13	2

* The gender within each age group has not been summarised

Table SIII.2. Person Exposure in malaria by ethnic or racial origin (Blinded Studies)

	Persons (n)		
	SP-C-005-06	SP-C006-06	SP-C-008-07
Asian/Oriental	127	228	15
Caucasian	0	0	0
Black	722	0	0
Total	849	228	15

Table SIII.3. Total Person Exposure by ethnic or racial origin – Company sponsored Phase II/III Completed studies in malaria

	Persons (n)
TOTAL (Phase II/pre-authorisation III)	2830
Asian/Oriental/Indian	1404
Black	1426

Demographic characteristics are summarised for all exposed persons from Phase II and pre-authorisation Phase III studies. The mean age was 20 years of age and ranged from 3 months to 60 years across groups. The majority of patients were males, split equally being of Black and Asian/Oriental (this category also included patients from India).

Phase IIIb/IV Studies

SP-C-013-11 WANECAM

SP-C-013-11 (WANECAM) was a comparative, randomised, multi-centre, open label parallel 3-arm clinical study (Phase IIIb/IV) to assess the safety and efficacy of repeated administration of PA or DHA-PQP 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's usual first line therapy. This study has been completed following the 2 year follow up in all patients. A first interim sub-study analysis has been performed, which provided an analysis of the safety and efficacy of repeat dosing with PA. The safety population consists of all PA patients dosed whereas the efficacy population includes those patients who were at sites where PA and AL were administered. This allowed for examination with comparable data from the phase III PA versus AL comparative pivotal studies. The study was undertaken in three West African countries which allows PYRAMAX to be tested over a number of malaria seasons in patients presenting with uncomplicated malaria. The sub-study analysis and clinical sub-study report formed 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. [redacted]

Table SIII.4. Demographic and Baseline Characteristics – SP-C-013-11 Study Population: Patients Randomised to the PYRAMAX Arm

Variable/ Statistic/Category	PYRAMAX (N=1342)	AL (N=671)	ASAQ (N=668)
Gender, n (%)			
Male	664 (49.5)	352 (52.5)	360 (51.3)
Female	678 (50.5)	319 (47.5)	308 (48.7)
Age (years)			
Available observations	1342	671	668
Mean	9.5	11.7	7.0
Standard deviation	8.0	9.63	5.65
Minimum	0	0	0
Q1	4	5	4
Median	8	9	6
Q3	12	15	9
Maximum	62	69	52
Age category, n (%)			
<18 years	1218 (90.8)	573 (85.4)	650 (97.3)
≤6 months	0 (0.0)	0 (0.0)	1 (0.2)
>6 months - <1 year	9 (0.7)	2 (0.3)	11 (1.7)
1-2 years	115 (9.4)	32 (5.6)	76 (11.7)
3-5 years	343 (28.2)	148 (25.8)	227 (34.9)
6-17 years	751 (61.7)	391 (68.2)	335 (51.5)
≥18 years	124 (9.2)	98 (14.6)	18 (2.7)
GRANULES sub-group*	PYRAMAX	AL	ASAQ
	(N=556)	(N=233)	(N=366)
Gender male/female	263/293 (47%/53%)	122/111 (52%/48%)	201/165 (55%/45%)
Age (years)			
Mean	4.1	4.4	3.8
Standard deviation	1.81	1.82	1.90
Minimum	0	0	0
Maximum	10	11	11

Variable/ Statistic/Category	PYRAMAX (N=1342)	AL (N=671)	ASAQ (N=668)
Age category, n (%)			
≤6 months	0 (0.0)	0 (0.0)	0 (0.0)
>6 months - <1 year	9 (1.6)	3 (1.3)	11 (3.0)
1-2 years	113 (20.3)	32 (13.7)	76 (20.8)
3-5 years	316 (56.8)	143 (61.4)	213 (58.2)
≥6 years	118 (21.2)	56 (24.0)	66 (18.0)
PK sub-group**			
Gender male/female	32/33 (49.2%/50.8%)		
Age (years)			
Mean	14.31		
Standard deviation	6.66		
Minimum	5.8 months		
Maximum	29.6 years		
Age category, n (%)			
<1 year, n (%)	29 (44.6%)		
≥1 year, n (%)	36 (55.4%)		

* The granules sub-group consists of all patients who received PYRAMAX granules from the Study versus AL and ASAQ
** PK subgroup treated for one episode only

The SP-C-013-11 study was 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.

Three analyses for **SP-C-013-11** were reported sequentially for this study:

- Sub-study interim analysis (safety of PA redosing)
- Second interim sub-study (comparing PA with AL and ASAQ)
- Final analysis

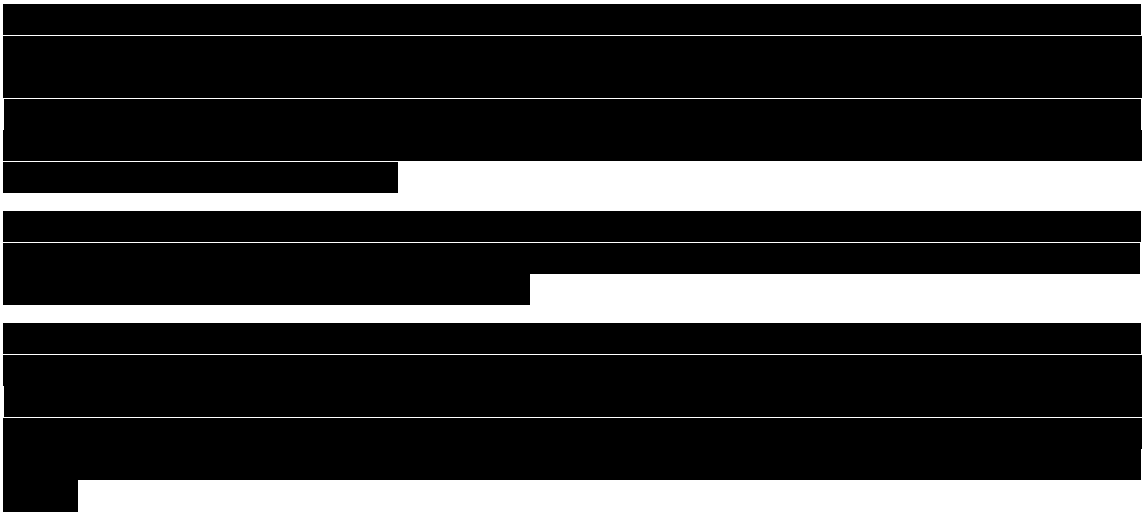


Table SIII.5. Patients taking Tablets or Granules in sub-study SP-C-13-11 (Final analysis)

Episode 1				
<20 kg		**≥20 kg**		**Total**
572		770		1342
Granules	**Tablets**	**Granules**	**Tablets**	
556 (97.2%)	16 (2.8%)	29 (3.8%)	741 (96.2%)	
Episode 2+				
<20 kg		**≥20 kg**		**Total**
393		434		827
Granules	**Tablets**	**Granules**	**Tablets**	
345 (87.8%)	48 (12.2%)	7 (1.6%)	427 (98.4%)	

Table SIII.6. Subject Disposition for repeated dosing – SP-C-013-11

(PYRAMAX and comparator for all patients and Granules – Final Analysis)

	ALL PATIENTS Pyronaridine artesunate	**Artemether lumefantrine**	**Artesunate amodiaquine**	**Total**	**GRANULES Pyronaridine artesunate**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients randomised	**1342 (100.0)**	**671 (100.0)**	**671 (100.0)**	**2720 (100.0)**	**591 (100.0)**
Patients treated (at least 1 dose)					
1 episode	1342 (100.0)	671 (100.0)	668 (100.0)	2681 (100.0)	556 (100.0)
2 episodes	827 (61.6)	447 (66.6)	389 (58.2)	1663 (62.0)	386 (69.4)
3 episodes	520 (38.7)	265 (39.5)	240 (35.9)	1025 (38.2)	271 (48.7)
4 episodes	307 (22.9)	161 (24.0)	134 (20.1)	602 (22.5)	194 (34.9)
5 episodes	183 (13.6)	84 (12.5)	82 (12.3)	349 (13.0)	128 (23.0)
6 episodes	95 (7.1)	44 (6.6)	38 (5.7)	177 (6.6)	72 (12.9)
7 episodes	52 (3.9)	24 (3.6)	14 (2.1)	90 (3.4)	40 (7.2)
8 episodes	21 (1.6)	12 (1.8)	5 (0.7)	38 (1.4)	15 (2.7)
9 episodes	10 (0.7)	3 (0.4)	1 (0.1)	14 (0.5)	8 (1.4)
10 episodes	2 (0.1)	2 (0.3)	1 (0.1)	5 (0.2)	2 (0.4)
11 episodes	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)	1 (0.2)
Patients who completed study	1236 (92.1)	619 (92.3)	623 (93.3)	2478 (92.4)	510 (91.7)
Withdrawn from study prematurely	106 (7.9)	52 (7.7)	45 (6.7)	203 (7.6)	46 (8.3)
During active treatment period	26 (1.9)	17 (2.5)	13 (1.9)	56 (2.1)	12 (2.2)
During post-treatment follow-up	77 (5.7)	34 (5.1)	31 (4.6)	142 (5.3)	34 (6.1)
Other time point	3 (0.2)	1 (0.1)	1 (0.1)	5 (0.2)	0 (0.0)
Reason for withdrawal					
Treatment failure	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.1)	0 (0.0)
Adverse event	11 (0.8)	1 (0.1)	3 (0.4)	15 (0.6)	7 (1.3)
Death	3 (0.2)	2 (0.3)	1 (0.1)	6 (0.2)	2 (0.4)
Protocol violation	7 (0.5)	4 (0.6)	0 (0.0)	11 (0.4)	4 (0.7)

	ALL PATIENTS Pyronaridine artesunate	Artemether lumefantrine	Artesunate amodiaquine	Total	GRANULES Pyronaridine artesunate
	n (%)	n (%)	n (%)	n (%)	n (%)
Lost to follow-up	19 (1.4)	7 (1.0)	6 (0.9)	32 (1.2)	5 (0.9)
Withdrawal of consent	48 (3.6)	20 (3.0)	30 (4.5)	98 (3.7)	22 (4.0)
Pregnancy	6 (0.4)	6 (0.9)	4 (0.6)	16 (0.6)	0 (0.0)
Study terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	12 (0.9)	9 (1.3)	1 (0.1)	22 (0.8)	6 (1.1)

In the final analysis, 2681 patients with acute, uncomplicated *Plasmodium* sp. malaria were eligible, randomised and treated for an initial episode of malaria; 1342 patients were randomised to the PYRAMAX arm 671 patients to the AL arm and 668 patients to the ASAQ arm. Of the 1342 patients with *P. falciparum* malaria treated at least once with PYRAMAX, 827 patients have had courses of PYRAMAX repeated at least once. 393 of the 572 patients, in the under 20 kg patient population, were dosed more than once over the analysis period, while in the 20 kg and over group 434 of 770 patients were dosed more than once. The median time between treatment episodes 1 and 2, episodes 2 and 3, episodes 3 and 4 reduced with repeat episodes after which the times between episodes were broadly similar. The median time between treatment episodes was longer for patients with body weight ≥20 kg than for patients with body weight <20 kg.

In the population of patients in the initial sub-study of SP-C-013-11 who received granules for oral suspension as treatment for the first episode of malaria, 591 were randomised to receive PYRAMAX, 233 to receive AL and 366 to receive ASAQ. During the analysis period, 351 were re-dosed with PYRAMAX A at least once and a further 220 at least twice. 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) were variable but broadly similar between the treatment arms (CSR Granules sub-study SP-C-013-11 Table 14.1.3).

Overall, the minimum time between treatment episodes in the PYRAMAX arm was 23 days (between episode 1 and episode 2) and the maximum time between treatment episodes was 440 days (between episode 3 and episode 4); however, the minimum time allowed before re-dosing per protocol was 28 days. As it is not possible to have real time PCR adjustment, recurrence of parasites before 28 days (28 day endpoint) is considered as a late treatment failure (i.e., recrudescence of the initial infection) and the patients was treated with a rescue therapy (quinine for 7 days or second line therapy) while after day 28, the recurrence was considered as a new infection and can be retreated with the initial treatment used.

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.

[redacted]

Note that the overall safety population has been taken to determine the exposure to PA and, after final data cleaning and database lock the number of patients exposed is slightly lower than reported in the second interim analysis; in the context of this study an additional 65 patients received three day doses of PYRAMAX for the purposes of a single site single treatment regimen assessment. In this group 29 of the 65 patients (44.6%) were <1 year of age and 41 patients (63%) were <10kg. These 65 patients are not included in the final number of patients exposed at least once to PA and are

reported separately. Therefore, the final number of PA exposed patients in study SP-C-013-11 is 1342.

SP-C-021-15

SP-C-021-15 was a Cohort Event Monitoring study designed to evaluate, in a real-life setting, the safety and tolerability in malaria patients of PYRAMAX. It was an open label non-randomised study was designed to assess the safety of PYRAMAX, particularly in patients with underlying liver function abnormalities and in patients with comorbidities such as HIV. In addition, enrolment of a cohort of approximately 2% children aged <1 year was included in order to assess the safety and tolerability of PYRAMAX in very young children. The study was undertaken in public health facilities of the CANTAM network in Central Africa and in West Africa where PYRAMAX was used as treatment for acute uncomplicated malaria, including repeat episodes.

The primary objective was the evaluation and identification of the hepatic safety events of PYRAMAX in a subgroup of patients enrolled with liver function tests (LFTs) >2x the Upper Limit of Normal (ULN) from blood taken immediately prior to treatment without any clinical signs or symptoms of hepatotoxicity and with signs and symptoms of uncomplicated malaria confirmed by a Rapid Diagnostic Test (RDT) or microscopy (thick blood smear). Secondary objectives included comparing the clinical hepatic safety of PYRAMAX between a cohort of patients enrolled with LFTs >2xULN and a cohort of patients enrolled with normal LFTs matched for demographic characteristics; evaluating the safety and tolerability in patients with normal and abnormal LFTs at inclusion (defined as an AST and/or ALT >2xULN prior to treatment), according to any possible hepatic underlying disease based on the finding of the hepatitis panel and according to their HIV status (where known), their nutritional status, their age (children <1 year of age in comparison to the rest of the treated population) and their weight; evaluating safety and tolerability in retreated patients with a special focus on hepatic safety; evaluating the potential for hypersensitivity reactions; evaluating the relationship between the occurrence of hepatic related adverse events (AEs) with or without LFT abnormalities and the administration of concomitant medications (in particular paracetamol, herbal medicines and antiretroviral drugs); and evaluating the "real-life efficacy" and compliance of PYRAMAX when used under usual conditions (including unsupervised medication intake) in patients with signs and symptoms of uncomplicated malaria confirmed by RDT or microscopy (thick blood smear).

The study planned to recruit, based on the primary objective, 120 malaria episodes in patients with baseline raised AST/ALT value >2xULN. This number of patients was needed for an 81.6% probability to observe one severe hepatic event in the target population. Given the screening rate in previous studies of 1.4% for malaria patients with AST/ALT >2xULN, it was planned that the recruitment of at least 8572 malaria episodes was required to meet the objectives of the study.

The total study duration for a single patient malaria episode was 28±2 days. To reflect the reality of repeat malaria episodes in a real-life setting, patients could be included more than once in the study. A washout period of at least 28 days was required between two consecutive treatments with PYRAMAX.

For each malaria episode, patients for whom a diagnosis of uncomplicated malaria (according to WHO criteria [2014]) was suspected underwent confirmation of infection by RDT/microscopy. Blood was taken for blood spot PCR analysis, and for retrospective LFT assessment and retrospective testing for viral hepatitis in patients determined to have abnormal LFTs only. A blood sample was to be taken for assessment of haematology parameters (with mandatory assessment of haemoglobin [Hb]). Assessments to determine eligibility for study inclusion were performed at the study centre or at one of the designated health care facilities on Day 0 during the initial consultation with the patient.

Treatment with PYRAMAX was administered based on body weight per the product label. Patients were instructed to take one PYRAMAX dose orally every 24 hours over a period of three consecutive days, i.e. on Day 0, then after 24 hours (on Day 1) and after 48 hours (on Day 2) from the first administration. The first dose of PYRAMAX was administered under Direct Observational Treatment (DOT) conditions at the health care facility, however subsequent doses of PYRAMAX were taken by the patient under usual conditions i.e. unsupervised medication intake at home.

All patients were instructed to contact the CHW or the designated study team member (STM) who was a medical physician, in the case of any AEs occurring within 28 days after the start of PYRAMAX administration. In the case of signs or symptoms of hepatotoxicity or hepatic related AEs, patients were referred to the study designated health care facility where blood samples were collected for assessment of LFTs, haematology parameters (Hb mandatory), and where appropriate, for full hepatitis panel assessment.

Female patients who became pregnant just before or after the start of the PYRAMAX treatment and for 2 months post-treatment were documented on the PYRAMAX Pregnancy Registry.

The study was subject to oversight by an independent study-specific Data Safety Monitoring Board (DSMB)

The study actually enrolled 7163 patients of whom 7114 were treated at least once. Of these treated patients prior to first treatment 6934 presented with normal LFTs, 158 presented with abnormal LFTs and 22 had unknown LFT status. Because some patients who had abnormal LFTs in one episode had normal LFTs in another, these patients were counted twice for the safety population. As a consequence, the safety population of 7154 patients consisted of 6961 with normal LFTs, 158 with abnormal LFTs and 35 whose LFT status was unknown. The 7114 patients overall received a total of 8560 treated episodes with 8367 treated episodes occurring in patients with normal LFTs at baseline, and 158 episodes occurring in patients with abnormal LFTs at baseline. (35 episodes had LFT status unknown). This number of episodes with abnormal LFTs increased the power to detect one hepatotoxic event to 89.2%.
There was an equal distribution of male and female patients in the Safety population overall (n=3569 [49.9%] male; n=3585 [50.1%] female), and across all the age group subcategories (Table 13).

All patients enrolled on study were ≥5 kg. Overall, 2634 (36.8%) patients weighed ≥5 kg - <20 kg and 4520 (63.2%) patients weighed ≥20 kg.

134 patients out of 7114 were aged <1 year (1.9%). Of these patients 124/134 (92.6%) had normal LFTs at baseline, and 9/134 (6.7%) had raised LFTs at baseline. (One out of 134 (0.7%) patient had unknown LFT status at baseline).

In terms of effectiveness, from a total of 7746 malaria episodes included in the PP population analysis, the Day 28 PCR-adjusted cure rate for the PP population was high at 98.6% (CI: 98.3, 98.9).

Analysis of the PCR-adjusted cure rate from 8480 episodes in the m-ITT population at Day 28 demonstrated treatment success of 90.9% (CI: 90.2, 91.5).

The Day 28 crude cure rate was 93.2% (CI: 92.6, 93.8) for the PP population and 85.9% (CI: 85.1, 86.6) for the m-ITT population.

Subgroup analysis by country demonstrated Day 28 PCR-adjusted cure rates ranging from 99.1% to 98.1% for the PP population, and from 97.0% to 80.2% for the m-ITT population, depending on the region and setting (rural or urban).

The Day 28 crude (unadjusted) cure rates ranged from 98.2% to 90.0% and from 96.1% to 73.7%, depending on country, for the PP and m-ITT populations, respectively.

All subgroups by age, nutritional status and formulation produced broadly similar efficacy results.

Overall, in this "real-life efficacy" study examining the effectiveness of PYRAMAX, the Day 28 cure rate was comparable to the parasitological cure rates reported in the three previous Phase 3 studies performed with either formulation against P. falciparum.

The number of patients treated at least once is shown in Table SIII.7

Table SIII.7. Subject Disposition for repeated dosing – SP-C-021-15 (Safety Population)

	Normal LFTs (N=6934)	Abnormal LFTs (N=158)	LFT Status Unknown (N=22)	Total (N=7114)
Patients with at least 1 episode, n (%)	6934 (100)	158 (100)	22 (100)	7114 (100)
Number of episodes per patient				
n	6934	158	22	7114
Mean (SD)	1.2 (0.58)	1.3 (0.70)	1.0 (0.00)	1.2 (0.58)
Number of episodes per patient, n (%)				
1	5916 (85.3)	130 (82.3)	22 (100)	6068 (85.3)
2	779 (11.2)	18 (11.4)	0	797 (11.2)
3	145 (2.1)	5 (3.2)	0	150 (2.1)
4	63 (0.9)	4 (2.5)	0	67 (0.9)
5	19 (0.3)	1 (0.6)	0	20 (0.3)
6	7 (0.1)	0	0	7 (0.1)
7	3 (0.0)	0	0	3 (0.0)
8	1 (0.0)	0	0	1 (0.0)
9	1 (0.0)	0	0	1 (0.0)

Source: Section 14.1, Table 14.1.4.2 SP-C-021-15.

Note: Normal LFTs: AST and ALT ≤2xULN at inclusion/enrolment; Abnormal LFTs: AST or ALT >2xULN at inclusion/enrolment. In case that the same patient appears in two of these columns (depending on the LFT baseline for each episode) the patient was classified as follows: normal and abnormal LFT – abnormal LFT only; normal LFT and LFT unknown -normal LFT only; abnormal and LFT unknown -abnormal LFT only.

The range in mean time between malaria episodes was similar for the PP and m-ITT populations, extending from 51 days to between ~126 - 129 days, depending on the analysis population. There was a tendency to shorter mean times between repeat malaria episodes with each additional episode. This difference in mean time between initial episodes and late recurrence of malaria is likely a reflection of the decreasing sample size as fewer repeat episodes occurred over time.

The disposition of the episodes is shown on Table SIII.8.

Table SIII.8. Subject Disposition of Episodes and Subjects – SP-C-021-15

	Normal LFTs		Abnormal LFTs		unknown LFTs		Total	
	n	%	n	%	n	%	n	%
Number of Screened Episodes							8918	
Number of Screen Failures							346	
Reason for Screen Failure								
Absence of Fever in the previous 24 Hours							10	
Anti-malarial intake before inclusion							43	
Complicated Malaria							14	
Consent Withdrawn							8	
Diagnosed negative for Malaria							24	
Inability to take an oral medication							6	
Known Pregnancy							9	
Lactating woman							21	
Patient could not comply with study schedule							4	
Patient was considered at particular risk when participating in the study							207	
Number of Enrolled Episodes	8369	100%	158	100%	82	100%	8609	100%
Number of Enrolled Subjects	6963	100%	158	100%	81	100%	7202	100%
Safety Population	8367	99.98%	158	100%	35	42.68%	8560	99.43%
Microbiological-ITT % Population	8290	99.06%	157	99.37%	33	40.24%	8480	98.50%
Per Protocol % Population	7589	90.68%	144	91.14%	13	15.85%	7746	89.98%
Subjects who Completed at least 1 Episode	6307	90.58%	140	88.61%	13	16.05%	6460	89.70%
Subjects who Discontinued at least 1 Episode	835	11.99%	18	11.39%	68	83.95%	921	12.79%
Reason for Discontinuation								
Adverse event/Serious AE	20	0.29%	0		1	1.23%	21	0.29%
Consent withdrawn	41	0.59%	1	0.63%	7	8.64%	49	0.68%
Insufficient therapeutic effect	24	0.34%	1	0.63%	0		25	0.35%
Patient lost to follow-up	612	8.79%	9	5.70%	10	12.35%	631	8.76%
Protocol violation/Non compliance	28	0.40%	3	1.90%	1	1.23%	32	0.44%
Death	3	0.04%	0		0		3	0.04%
Screen failure	0		0		39	48.15%	39	0.54%
Other	107	1.54%	4	2.53%	10	12.35%	121	1.68%
Administration of Rescue Treatment	27	0.39%	2	1.27%	10	12.35%	39	0.54%
Insufficient Therapeutic Effect	1	0.01%	0		0		1	0.01%
Non-Adherence to Drug Regimen	77	1.11%	2	1.27%	0		79	1.10%
Out of Window Visit	2	0.03%	0		0		2	0.03%

SP-C-026-18

This was a randomised, open-label, three-arm, outpatient study in asymptomatic individuals from the Gambia and Zambia with P. falciparum mono-infection confirmed at baseline. A total of 300 participants who were >5 years of age and >20 kg body weight were to be randomised into the study (n=100 participants in each of three treatment arms) in order to assess the efficacy and safety of three dosing regimens (3 days, 2 days or 1 day) of the fixed-dose Artemisinin-based Combination Therapy PYRAMAX.

Consenting participants who passed pre-screening, had a second pre-dose blood smear taken and participants with confirmed P. falciparum mono-infection with a parasite density between 20/µL and 50,000/µL who fulfilled all the study entry criteria were enrolled and randomised 1:1:1 to receive treatment with Pyramax orally for 3 days, 2 days or 1 day (Treatment Arms A, B and C, respectively).

All participants were followed until Day 63 (counted from initiation of dosing as Day 0). Blood samples were collected on Days 0, 1, 2, 3, 7, 14, 21, 28, 35, 42 and 63 for malaria diagnostics, assessment of parasite density and qPCR analysis.

Safety and tolerability to treatment was assessed in all study participants throughout the study.

Optional participation in a pharmacokinetic sub-study where blood samples were collected for the measurement of artesunate (AS)/ dihydroartemisinin (DHA) and pyronaridine was also included.

In terms of efficacy, overall, the Day 28 PCR-adjusted APR for the PP set using the WHO-validated method was 100% for Treatment Arm A (3-day regimen) and Treatment Arm B (2-day regimen). PCR-adjusted APR at Day 28 dropped slightly in participants in Treatment Arm C (1-day regimen) compared to the other treatment arms, however efficacy with the Treatment Arm C (1-day regimen) was still high at 96.8%.

The disposition of the patients in this study is shown in Table SIII.9.

Table SIII.9. Subject Disposition of Episodes and Subjects – SP-C-026-18

	3-day regimen (Arm A) n (%)	2-day regimen (Arm B) n (%)	1-day regimen (Arm C) n (%)	Overall n (%)
Participants randomised	101 (100.0)	100 (100.0)	102 (100.0)	303 (100.0)
Participants treated	101 (100.0)	100 (100.0)	102 (100.0)	303 (100.0)
Participants completed	98 (97.0)	93 (93.0)	100 (98.0)	291 (96.0)
Withdrawn from study prematurely	3 (3.0)	7 (7.0)	2 (2.0)	12 (4.0)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Lost to follow-up	1 (1.0)	3 (3.0)	1 (1.0)	5 (1.7)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Site terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by subject	1 (1.0)	4 (4.0)	1 (1.0)	6 (2.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Phase IIIb/IV Investigator initiated studies

Studies SP-C-022-17 and SP-C-024-17 were Phase IIIb/IV investigator-initiated studies, which had been recorded in the previous version of this RMP. Although study codes (using the same nomenclature as sponsored studies) were assigned, these studies were conducted entirely independently from the SOH, and no safety or efficacy data has been incorporated from the studies into the SOH clinical or safety databases. The studies have all completed and the summary of two of the studies is presented below.

Clinical Trial ID (Regulatory Reference No.)	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	FPFV	Planned Enrolment	Cumulative exposure
SP-C-022-17	Phase IIIb/IV	Vietnam	Evaluation of therapeutic effectiveness and safety of pyronaridine artesunate in an area of artemisinin resistance in Vietnam	Open label WHO TES study conducted at 5 sites	Pyronaridine-artesunate: depending on body weight, 1 to 4 fixed combination tablets of pyronaridine: artesunate (180:60 mg)	Patients with acute uncomplicated falciparum malaria.	10 May 2017	170 (estimated)	155 patients PUBLISHED

Published: Pyronaridine-artesunate efficacy and safety in uncomplicated *Plasmodium falciparum* malaria in areas of artemisinin-resistant falciparum in Viet Nam (2017-2018). Bui Quang P[1], Huynh Hong Q[2], Tran Thanh D[1], Le Thanh D[3], Nguyen Quang T[1], Truong Van H[1], Khim N[4], Witkowski B[4], Cong DT[5], Bustos MD[6], Ringwald P[7], Ta Thi T[1]. Clin Infect Dis. 2019 Jun 28. pii: ciz580. doi: 10.1093/cid/ciz580.

Clinical Trial ID (Regulatory Reference No.)	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	FPFV	Planned Enrolment	Cumulative exposure
SP-C-024-17	Phase IIIb/IV	Cambodia	Efficacy and safety of pyronaridine-artesunate plus single-dose primaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in eastern Cambodia	Open label WHO TES study conducted at 2 sites	Pyronaridine-artesunate: depending on body weight, 1 to 4 fixed combination tablets of pyronaridine: artesunate (180:60 mg)	Patients with acute uncomplicated falciparum malaria.	Aug 2017	120 (estimated)	121 patients PUBLISHED

Published: Efficacy and Safety of Pyronaridine-Artesunate plus Single-Dose Primaquine for Treatment of Uncomplicated *Plasmodium falciparum* Malaria in Eastern Cambodia.
Leang R[#1], Mairet-Khedim M[#2], Chea H[1], Huy R[1], Khim N[2], Mey Bouth D[3], Dorina Bustos M[4], Ringwald P[5], Witkowski B[2] Antimicrob Agents Chemother. 2019 Feb 26;63(3). pii: e02242-18. doi: 10.1128/AAC.02242-18. Print 2019 Mar.

The clinical studies which comprise the clinical development programme for PYRAMAX are summarised in Annex 2.

The tables below show the estimated cumulative subject exposure split by ethnicity and by age in the PYRAMAX company-sponsored phase I-III clinical trial programme. This data is unchanged from the previous RMP.

The table below show the estimated cumulative subject exposure to pyronaridine-artesunate from company-sponsored Phase I-III clinical trials by age and gender.

Table SIII.10. Age Group and Gender (Phase I to III)

	Persons (n)	
TOTAL (Phase I) all > 18 years of age	307	
TOTAL (Phase II/III)	2830	
Age group (years of age)		
< 1	9	
1-<5	173	
5-12	704	
> 12-<18	402	
≥ 18	1542	
Gender	M	F
Phase I	145	115
Phase II/III	1872	958

Table SIII.11. Person Exposure by age group and gender for Phase IIIb/IV studies

	SP-C-013-11[a]		SP-C-020-15[b]		SP-C-021-15		SP-C-026-18	
TOTAL (treated with PYRAMAX)	1342		101		7154[c]		303	
Age group (years of age) PYRAMAX only								
<1	9		0		134		0	
1 - <3	107							
1 - <5			31		1711		0	
3 - <6	335							
5 - <18			70		3609		226	
6 - <18	735							
≥18	117		0		1700		77	
Gender	M	F	M	F	M	F	M	F
	664 (49.5%)	678 (50.5%)	53 (52.5%)	48 (47.5%)	3569 (49.9%)	3585 (50.1%)	148 (48.8%)	155 (51.2%)

a Does not include the 65 patients in the PK subgroup

b SP-C-020-15 is a TES study but is included here as the breakdown of ages was available

c Although 7114 patients were treated at least once, the safety population consists of 7154 patients because a patient was considered differently if they fell into more than one LFT category. Therefore, if a patient had an adverse event with normal baseline LFTS for events in any episode with that category then they were counted

only once. However, if an episode had a different LFT category they were then counted again for that category. This occurred on 40 occasions.

Table SIII.12. Person Exposure by Ethnic Origin for Phase I to IV malaria studies

	Persons (n)
TOTAL (Phase I)	307
Asian	169
Caucasian	119
Hispanic	15
Black or African American	1
TOTAL (Phase II/III)	2830
Asian/Oriental/Indian	1404
Black or African American	1426
TOTAL (Phase IIIb/IV/TES)	9405
Asian/Oriental/Indian/Caucasian (TES)	581 (60+123+176+121+101)[a]
Black or African American	8824 (1342[b] + 65[c] + 7114[d]+ 303[e])
Total Phase I-III	3137
Total Phase IIIb/IV/TES	9405
TOTAL All Studies	12542

a Studies SP-C-018-13 n=60, SP-C-019-14 n=123; SP-C-022-17 n=176; Study SP-C-024-17 n=121; SP-C-020-15 n=101
b SP-C-013-11 main study: 3360 Episodes
c SP-C-013-11 PK sub-study patients
d SP-C-021-15 (CANTAM) completed: 8560 Episodes
e SP-C-026-18 completed

[redacted]

[redacted]

PYRAMAX in pregnancy

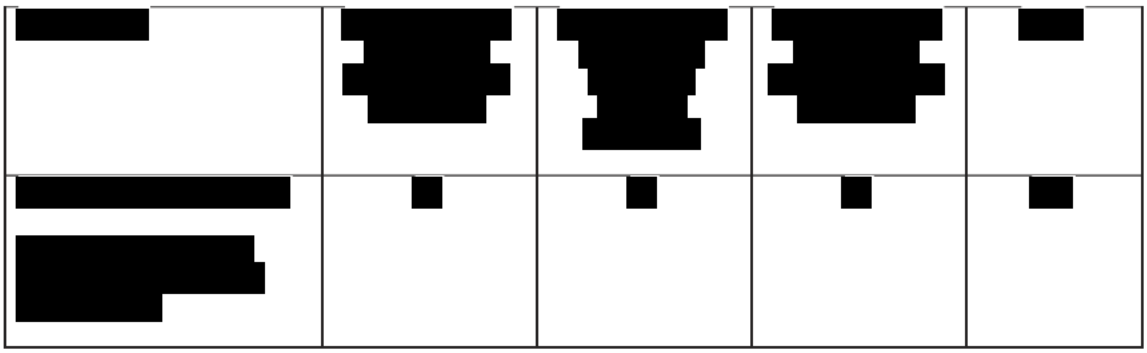
- **PYRAPREG Trial:**

Efficacy and safety assessment of pyronaridine-artesunate for the treatment of *P. falciparum* uncomplicated malaria in African pregnant women (PYRAPREG) is ongoing as a Phase 3, non-inferiority, randomised, open-label clinical trial (Djimde M et al. BMJ Open 2023;13). This trial is sponsored independent of the SOH.

[redacted]	[redacted]
[redacted]	[redacted]

- **MiMba Trial:**

The PYRAMAX MiMBa Observational Registry is ongoing in Kenya and Burkina Faso which is sponsored by University of Liverpool, UK.



Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion 1: Known hypersensitivity to pyronaridine or artesunate or any component of the formulation

Is it considered to be included as missing information: No.

Reason for exclusion: Standard contraindication condition.

Criterion 2: Underlying hepatic injury or significant liver function test abnormalities

Is it considered to be included as missing information: No.

Reason for exclusion: SmPC proposes to recommend liver function testing in patients with known liver disease or with signs or symptoms of liver disease or who are on concomitant medication with hepatotoxic potential. Additionally, patients with clinical signs or symptoms of hepatic injury or known severe liver disease are contraindicated. Evidence from a post approval study (SP-C-021-15) shows that patients with known asymptomatic ALT or AST >2xULN prior to treatment do not develop any symptomatic hepatotoxicity.

Criterion 3: Significant increase in liver transaminases related to the administration of pyronaridine

Is it considered to be included as missing information: No.

[redacted]

[redacted]

Criterion 4: Severe renal impairment

Is it considered to be included as missing information: No.

Effect of exclusion: None anticipated but theoretically pyronaridine level could be marginally higher but there are two paths of final elimination faecal and renal of which renal is the lesser path. Nonetheless, severe renal impairment is a contraindication.

Exclusion criteria which were not included as contraindications in the approved SmPC are described in section SIV.3.1 with the justification for each item described in SIV.3.1.1 - SIV.3.1.10.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Limitations of ADR detection common to clinical trial development programmes.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare (it may be appropriate to choose other ADR frequencies)	[redacted]	[redacted]
Due to prolonged exposure	Not applicable as single 3-day courses with proposed minimum of 28 days between dosing.	
Due to cumulative effects	The Phase I-III study programme had identified raised liver enzymes as a potential concern with repeated dosing which suggested that liver is a target organ for safety.	This concern has been addressed through data from two phase IIb/IV studies: In the repeat dose longitudinal study (SP-C-013-11) in which just over half the 1342 enrolled PYRAMAX patients were re-dosed (following a repeat malarial infection, within 60 days and 75% within 90 days, which is within 5 half-lives of pyronaridine. The pattern of transaminase rises with repeated dosing in this study was similar to that seen following a single treatment course in the original study programme. The cohort event monitoring study (SP-C-021-15) enrolled 7114 patients with 797 (11.2%) patients treated for at least 2 episodes (each episode being a minimum of 28 days, with retreatment up to a maximum of 9 malaria episodes occurring in 1 patient. Data from both studies confirm the findings of no increased risk of raised enzymes on repeat administration. In addition, study SP-C-026-18 assessed the safety and efficacy of one, two and three days of dosing in patients with

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
		asymptomatic *P falciparum*, parasitaemia. In this study, there was no evidence of an increase in adverse events or rises in liver function tests between the three dosing regimens. Ongoing post marketing pharmacovigilance will also capture hepatotoxicity and serious adverse events on repeat dosing.
Which have a long latency	Not applicable to this programme.	Adverse events of changes in laboratory values tend to occur early and reverse quickly even within 5 half-lives of pyronaridine.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The applicant has been granted a positive Opinion under EU-M4all (Article 58) of Regulation (EC) No. 729/2004 for the treatment of acute uncomplicated *P. falciparum* malaria and blood stage *P. vivax* malaria in patients 5 kg or greater weight. For the pivotal and key supporting studies, the exclusion criteria are listed in the table (Table SIV.1) below. The studies included males and females of Black or Asian ethnicity for tablets greater than 20 kg weight with confirmed diagnosis of malaria.

Infants, both male and female of Black or Asian ethnicity, greater than 5 kg and less than 20 kg were studied with a granule formulation of PYRAMAX.

Key exclusion criteria pertaining to safety are addressed by the contraindications, warnings and precautions for use in the summary of product characteristics (SmPC). Those exclusion criteria that are not covered in the SmPC were designed to enhance interpretability of the study data. These are not considered applicable to the prescribing information and are thus not included in the proposed SmPC such as the use of antibacterial agents with anti-malarial activity, febrile illnesses or recent investigational drug (if appropriate).

Table SIV.1. Exclusion Criteria Across the Completed Development Programme

Study number	No of patients exposed to PYRAMAX	Age range	Exclusion criteria for study
SP-C-002-05 (Phase II)	[redacted]	15-60	• Previous participation in the Phase II study or any study of PYRAMAX at Phase III • Mixed plasmodium infection • Signs and symptoms of severe malaria as defined by WHO Criteria 2000 • Severe malnutrition (defined as a child whose weight-for-height is below -3 standard deviations or less than 70% of the median of the NCHS/WHO normalised reference values)

Study number	No of patients exposed to PYRAMAX	Age range	Exclusion criteria for study
SP-C-003-05 (Phase II)	[redacted]	2-14	• Known history or evidence of clinically significant disorders, such as cardiovascular (including arrhythmia, QTc interval ≥ 450 milliseconds); respiratory (including active tuberculosis); history of jaundice, hepatic, renal, gastrointestinal, immunological (including active human immunodeficiency virus [HIV]-acquired immune deficiency syndrome), neurological (including auditory), endocrine, infectious, malignancy, psychiatric; and history of convulsions or other abnormality (including recent head trauma) • Severe vomiting, defined as more than three times in the 24 hours prior to inclusion in the study or inability to tolerate oral treatment, or severe diarrhoea defined as three or more watery stools per day • Presence of significant anaemia, as defined by Hb <8 g/dL. (Phase III only) • Known history of hypersensitivity, adverse reactions or allergy to pyronaridine, artesunate or other artemisinins • Use of any other antimalarial agent within 2 weeks prior to start of the study as evidenced by positive urine test • Patients taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (flecainide, metoprolol, imipramine, amitriptyline, clomipramine) (Phase III only) • Known active Hepatitis A IgM (HAV-IgM), Hepatitis B surface antigen (HbsAg) or Hepatitis C antibody (HCV Ab) • Known seropositive HIV antibody • Liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] levels) >2.5xULN • Known significant renal impairment, as indicated by serum creatinine level >1.4 mg/dL (≥2 in study SP-C-003-05) • Received an investigational drug within the 4 weeks prior to the screening visit (8 weeks for study SP-C-003-05) • Presence of febrile conditions caused by diseases other than malaria. • Pregnant and breastfeeding females. • Patients with known disturbances of electrolytes balance, e.g., hypokalaemia or hypomagnesaemia • Presence of other clinical condition requiring hospitalisation. (Studies SP-C-006-06; SP-C-008-07) • Receipt of antibacterial with known anti-malarial activity in the preceding 2 weeks (Studies SP-C-006-06; SP-C-008-07) • Known history of hypersensitivity, allergic, or adverse reactions to chloroquine, primaquine, and related agents (Study SP-C-008-07) • Previous participation in the clinical study with PYRAMAX (Study SP-C-008-07)
SP-C-004-06 (Phase III)	[redacted]	4-60	
SP-C-005-06 (Phase III)	[redacted]	5-60	
SP-C-006-06 (Phase III)	[redacted]	7-60	
SP-C-007-07 (Phase III)	[redacted]	3m-11	
SP-C-008-07 (Phase III)	[redacted]	17-56	

Study number	No of patients exposed to PYRAMAX	Age range	Exclusion criteria for study
SP-C-013-11	[redacted]	6m-62	• Patients with signs and symptoms of severe/complicated malaria requiring parenteral treatment according to the WHO criteria (2000). 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 Known history or evidence of clinically significant disorders such as cardiovascular (including arrhythmia, QTc interval ≥450 msec, respiratory, history of jaundice, hepatic, renal, gastrointestinal, immunological, neurological, endocrine, infectious, malignancy, psychiatric, history of convulsions, or any other abnormality (including recent head trauma) • Presence of significant anaemia, as defined by haemoglobin <7 g/dL • Presence of febrile conditions caused by diseases other than malaria at the first inclusion and if oral treatment was not possible for the subsequent episode • 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 • Use of any other antimalarial agent, including traditional medicines known to have antimalarial properties, within 2 weeks prior to the start of the study • Female patients of child-bearing potential (≥12 years) were to be neither pregnant (as demonstrated by a negative pregnancy test) or lactating, and not planning on becoming pregnant during the 42-day period after treatment • Received an investigational drug within the previous 4 weeks • Known or suspected chronic alcohol abuse, >3 units/day in men and >2 units/day in women • Known active hepatitis A antibody, hepatitis B surface antigen, or hepatitis C antibody • Known positive for HIV antibody • Liver function tests (LFT; ALT levels) >2xULN (upper limit of normal range; this criterion was amended during the study conduct) • Known significant renal impairment, as indicated by serum creatinine of >1.5xULN
SP-C-020-15	[redacted]	1-12	• Complicated or severe malaria, • Non-*P. falciparum* or mixed *Plasmodium* infection • History of hepatic and/or renal impairment • Any clinically significant illness other than malaria, anaemia with a haemoglobin (Hb) concentration

Study number	No of patients exposed to PYRAMAX	Age range	Exclusion criteria for study
SP-C-021-15	[redacted]	3m-89	• Patients with clinical signs or symptoms of hepatic injury (such as nausea, abdominal pain associated with jaundice) or known severe liver disease (i.e. decompensated cirrhosis, Child-Pugh stage 3 or 4). • Known allergy to artemisinin and/or to pyronaridine. • Known pregnancy. • Lactating women were to be excluded if other anti-malarial treatments were available. • Complicated malaria as per WHO 2012 definition • Patients that the Investigator considered would be at particular risk if in receipt of an anti-malarial or through participation in the study. • Patients having been treated with Pyramax in the previous 28 days.
SP-C-026-18	[redacted]	6-64	• Haemoglobin <7 g/dL (measured at screening) • History of having received any antimalarial treatment (alone or in combination) during the following periods before screening: 1. Piperaquine, mefloquine, naphthoquine or sulfadoxine-pyrimethamine within 6 weeks prior to screening 2. Amodiaquine, chloroquine within 4 weeks prior to screening 3. Any artemisinin derivative (AS, artemether or DHA), quinine, lumefantrine or any other antimalarial treatment or antibiotic with antimalarial activity (including cotrimoxazole, tetracyclines, quinolones and fluoroquinolones and azithromycin) within 14 days prior to screening • Any herbal products or traditional medicines during the 7 days prior to screening (if spontaneously reported by the participant) • Known allergy to the study drugs (pyronaridine and/or any artemisinin derivatives) • Positive urinary pregnancy test for women of reproductive age • Lactating women • Evidence of severe malnutrition, defined as follows for the specified age-groups: 1. Participants aged ≥20 years: BMI <16 kg/m^2 2. Participants aged <20 years: BMI-for age z-score <-3 • Participation in other studies within 30 days before the beginning of the current study and/or during study participation • Inability to comprehend and/or unwillingness to follow the study protocol • Previously randomised in this study • Severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results

Study number	No of patients exposed to PYRAMAX	Age range	Exclusion criteria for study
			• Examples would include but are not limited to: 1. Immunological disorders (including known seropositive HIV antibody), 2. Severe psychiatric disorders 3. Clinical signs or symptoms of hepatic injury • Participant the Investigator considers would be placed at particular risk should they receive an antimalarial or participate in the study.

[redacted]

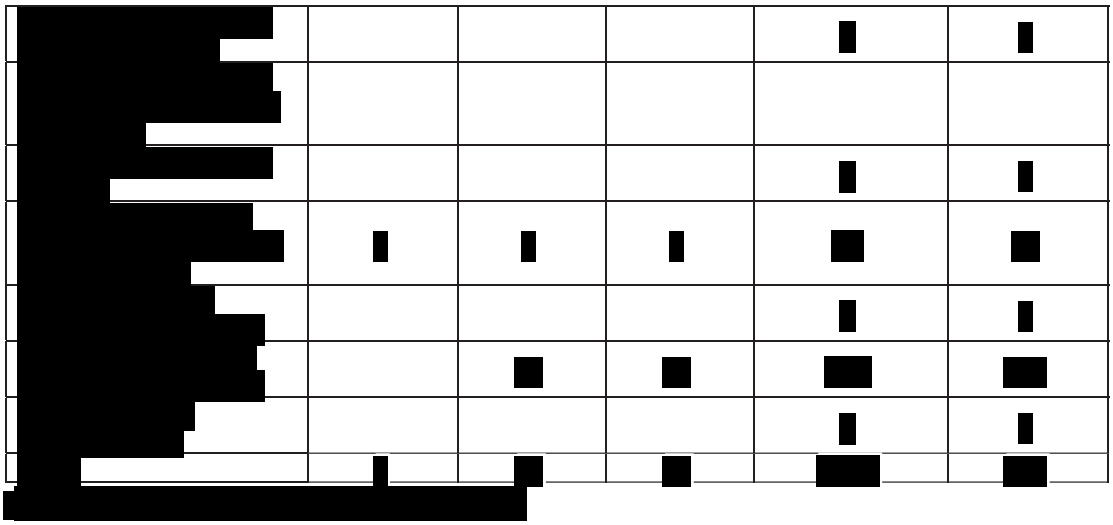
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



1 Children

Children were an important part of the clinical trial programme, with children as young as 2 years of age treated as part of the programme with tablets and children as young as 3 months treated as part of the programme with granules. In all pre and post authorisation studies to date pre-term new-borns, neonates or infants <5 kg (approximately 3 months of age) have not been treated with PYRAMAX.

In the pre-authorisation programme, Study SP-C-007-07, where granules were used, children as young as 3 months were included. However, the overall number of children under 1 year of age was low. Results are available from other 5 studies that enrolled children under 12 years of age. These consisted of a Phase II, paediatric dose finding study (SP-C-003-05) and three Phase III studies in adults and children (SP-C-004-06, SP-C-005-06 and SP-C-006-06) and a Phase III paediatric study (SP-C-007-07). The numbers exposed are presented in section SIII.

More information on patients weighing less than 20 kg treated with a paediatric formulation of granules for oral suspension has been developed specially targeting the younger patients. This was studied in the Phase II study (cohort 4) SP-C-003-05, the pivotal trial SP-C-007-07 as well as in the post authorisation clinical trials Studies SP-C-013-11 and SP-C-021-15, which investigated the efficacy and safety of repeat courses of PYRAMAX in adults and children.

The pivotal study SP-C-007-07 was conducted in seven clinical sites in Africa and Philippines (Kayentao et al., 2012). PYRAMAX granules were compared to crushed AL tablets in a non-inferiority design study. The dose range received by subjects was 3.67-17.20 mg/kg/dose for artesunate and 11.01-51.61 mg/kg/dose for pyronaridine; and 2.0-16.44 mg/kg/dose for artemether and 12.0-98.63 mg/kg/dose for lumefantrine. 355 patients, with a median age of 5 years (range 0.3 – 11 years) received PYRAMAX granules, while 180 patients with a median age of 5 years (range 0.3 – 12 years) received crushed AL tablets. PYRAMAX was shown to be at least as effective and safe as AL for the treatment of patients ≤ 12 years of age with acute, uncomplicated *P. falciparum* malaria: PCR-corrected ACPR at Day 28 was

demonstrated to be statistically significantly > 90% in the PYRAMAX group (97.1%). Non-inferiority of PYRAMAX compared with AL was concluded for both PCR-corrected on Days 14, 21, 28 and 35 in the EE and ITT populations. No clinically important differences in Day 28 PCR-corrected ACPR were observed by centre, age, gender, or previous episode of malaria. Time to parasite clearance was marginally statistically significantly (p=0.0459) shorter in the PYRAMAX group compared with the AL group.

The median age of the patients in all of the adult and children Phase II/III varied from 13 years in SP-C-005-06 to 23 years in Study SP-C-004-06 and 25 years in SP-C-006-06 and the adult-only Phase II study SP-C-002-05.

[redacted]

In the Phase IIIb/IV SP-C-013-11 study recruited 2671 adults and children, the median age of children treated was 8 years of age and 1218 (90.8%) patients treated with PYRAMAX were under 18 years of age. Of those patients who received PYRAMAX granules for treatment of their first episode [n= 572 (42.6%)] were <20 kg in weight.

Overall, in the study population there were 585 PYRAMAX patients treated with granules in episode 1 of whom 43 weighed <10 kg.

In the Phase IIIb/IV SP-C-021-15 cohort study the median age of all patients included in the safety population (n=7154) was 9.0 years (range 0-89 years). Patients with abnormal LFTs at inclusion/enrolment had a median age of 4 years (range 0-68 years) compared to a median age of 9.0 years (range 0-89 years) and 6 years (range 0-50 years) in patients with normal LFTs and those with unknown LFT status, respectively, at inclusion/enrolment.

There was an equal distribution of male and female patients in the safety population overall (n=3569 [49.9%] male; n=3585 [50.1%] female), and across all the age group subcategories.
All patients enrolled into the study were ≥5 kg. Overall, 2634 (36.8%) patients weighed ≥5 kg - <20 kg and 4520 (63.2%) patients weighed ≥20 kg.

A total of 134 (1.9%) of all patients enrolled on the study were aged <1 year. Of these, 9 (5.7%) patients aged <1 year had abnormal LFTs at inclusion/enrolment, compared to 124 (1.8%) patients in this age group with normal LFTs and 1 patient aged <1 year with unknown LFT status at inclusion/enrolment.

This information provides reassurance given that this patient population of young children have been previously under-represented in the PYRAMAX clinical programme conducted and that the acceptable safety profile remains consistent.

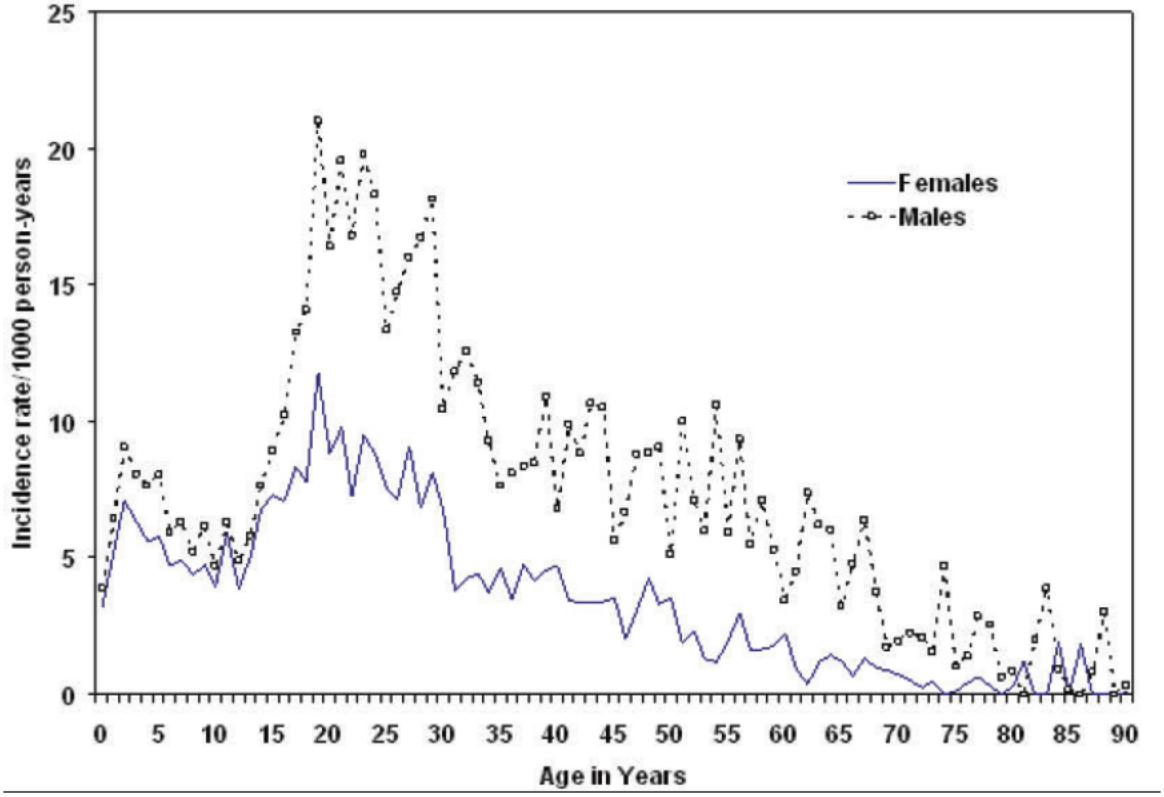
2 Elderly

There was no upper age limit for recruitment in study SP-C-021-15 with adults up to 89 years of age enrolled. The median age for PYRAMAX patients enrolled in the pre-authorisation clinical studies was 18.9 years. The ratio of patients under 25 to those 25 or over was approximately 2:1. [redacted]

However, malaria is not a disease of the older age groups to the extent that it occurs in young adults and children (See Figure 7 as an example (Yeshiwondim AK et al. 2009)).

The safety in older patients will continue to be monitored through pharmacovigilance, the overall study population reflecting the low numbers of older people that require treatment for malaria.

Figure 7 Malaria incidence rate (per 1000 person-years) by age and gender in East Shoa, Ethiopia



3 Malnourished children

Patients with severe malnutrition were excluded in the pre-authorisation studies. Malnourished patients represent a treatment challenge. Additionally, severe malnutrition is associated with depleted glutathione and this may increase the risk of hepatotoxicity which reduces the treatment options of any treatment which may have an effect on liver function.

Malnourishment status was not an exclusion criterion in the recently completed Phase IIIb/IV cohort study (SP-C-021-15 CANTAM). 370 (5.2%) patients in the study were determined to be malnourished at inclusion/enrolment. [redacted]

Nutritional status is therefore not considered to influence outcome.

There were no differences in the incidence of adverse events in the study based on nutritional status.

4 Severe malaria

It is not known how effective PYRAMAX is in the treatment of severe malaria. PYRAMAX is an orally formulated tablet **or granule** and there are as yet no plans to develop an *iv* formulation for the purposes of treating severe malaria. Patients with severe malaria were excluded from the studies and while

hyperparasitaemia associated with severe malaria may be defined as a parasite density of >200,000/µL (WHO definition) relatively few patients who received PYRAMAX (27/2815 [1%]) **fell** into this category, all **those who did, had** *P. falciparum* infection. From the safety perspective ≥ 80,000 parasites per µL was used in order to explore any influence of hyperparasitaemia on safety. From an efficacy perspective in the hyperparasitaemia subgroup, there were no early treatment failures. Late clinical failures only started to appear at Day 35 with late parasitological failures occurring in small numbers from Day 14, rising to 2.2% at Day 35. However, it is not possible to make a statement as to the overall efficacy of PYRAMAX in severe malaria based on these data.

In all of the studies patients who presented with severe malaria were excluded and, if as a result of the evolution of the malaria or parasitaemia assessed after the first dose of PYRAMX was administered the patient was diagnosed with severe malaria they were withdrawn from the study.

5 Pregnancy and breast feeding

Pregnant and breast-feeding patients were specifically excluded from the main trial programme and currently PYRAMAX is only being recommended for patients who are pregnant in second and third trimesters and only if no other anti-malarial treatment is considered suitable and in the first trimester, only for life-threatening situations.

In line with CHMP commitments, a pregnancy register was established for the PYRAMAX after the initial "positive opinion" by EMA and the periodic update reports from the pregnancy registry have been submitted. The most recent pregnancy registry report number 6 was submitted for review by EMA in February 2024 to cover the previous 3-year reporting period. In all company sponsored clinical trials and in the sales of PYRAMAX in Korea and Africa, as outlined in the Article 58 Scientific Opinion application, unintended exposure during pregnancies which are brought to the attention of the Sponsor are reported according to the principles outlined in the protocol SP-PV-012 for the assessment of the safety of antimalarial drug use during pregnancy. The protocol outlines the processes for data capture and reporting of information on pregnancies. Furthermore, in order to provide additional information on pregnancy exposure, additional maternal and neonatal data elements may be sought where possible from the attending healthcare worker.

Inadvertent pregnancy during treatment with PYRAMAX for malaria was monitored in clinical trials.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Conclusions for PYRAMAX exposure in pregnancy:

Inadvertent pregnancy during treatment with PYRAMAX for malaria was monitored in Sponsor clinical trials and where commercially available in line with the procedure outlined in protocol SP-PV-01-12, during the reporting period to January 31st 2024.

Further data have been acquired over the reporting period with the conduct of two sizable well-structured research projects which include PYRAMAX exposure in pregnant women. Both the MiMBa pregnancy registry and the PYRAPREG are conducted with well-established and respected research consortia who are highly experienced in studying the treatment of malaria in pregnant women. With both initiatives still ongoing the data are regarded as interim; however, the impact of the work has substantially improved the opportunity to examine how PYRAMAX exposure both for treating the malaria infection and also providing more information on its safety profile in both the mother and offspring. The endpoints and outcomes include those of malaria efficacy as well as pregnancy outcome and safety of PYRAMAX treatment in this population. The follow up of those babies born following exposure in these controlled settings will further provide reassurance in relation to any longer-term effects, as secondary or exploratory outputs.

The data collected to date on the use of PYRAMAX in pregnant women with uncomplicated malaria, can be considered to be encouraging and do not lead to an increase in adverse pregnancy outcomes, while these preliminary data suggest that pregnancies losses are reduced by reducing the morbidity of untreated malaria.

There are no data on exposure in breast-feeding patients.

6 Safety and patient with parasitaemia ≥ 80,000/µL

A safety review of patients who entered the Phase II/III studies with a parasite count of ≥80,000/µL was undertaken with the objective of determining whether there were increased safety risks for this subgroup compared with the population as a whole (Module 5.3.5.3.3). Only patients in the *P. falciparum* studies are included as no patients had a *P. vivax* count of ≥80,000/µL and 11.1% of PYRAMAX, 11.3% of MQ + AS and 14.3% of AL patients fell into this category. The summary of findings was as follows:

Overall, there were few differences in safety between the high parasite load subgroups and the whole population.

Although there were a slightly greater proportion of patients with at least one adverse event in all of the treatment groups adverse events which might signal a safety issue for the treatment of PYRAMAX (or the comparators) in as much as the higher parasite count might exacerbate these events, there appeared to be no difference in the high parasite load subgroup compared with the whole population.

In terms of specific findings, differences between the subgroup and the whole population were small, with AEs such as AST, fever and vomiting having proportionally slightly higher incidence for the subgroup as might be expected from the greater parasite burden. The higher baseline parasite count would also have accounted for the higher baseline bilirubin and AST values as well as the proportionally greater fall in haemoglobin on treatment. However, the findings were similar for all anti-malarial treatments. There was no greater incidence of cardiac events or ECG findings in patients with a high parasite load compared with the total patient population. As there were no patients with a parasite load ≥80,000/µL in the *P. vivax* study, there are no data for chloroquine treated patients.

Therefore, the effects of PYRAMAX (and the comparators used) did not appear to be associated with a significant risk specifically with regard to increased adverse events, liver function abnormalities or ECG changes in patients with a higher parasite load.

7 Patients with hepatic and renal impairment

Patients with significant ongoing or untreated abnormalities in renal or hepatic function that may interfere with the ability to complete a study or the evaluation of safety were excluded from the clinical studies. No patients were enrolled with established hepatic impairment, although many patients had raised bilirubin and AST levels on entry which is related to their malaria rather than hepatic function (Echeverri M et al. 2003). In the vast majority of cases these values fell during the course of the study. The non-clinical data indicate that pyronaridine is primarily excreted in the faeces whereas 56% of the DHA the metabolite of artesunate was excreted in the urine. Therefore, while there may be limited effect of renal impairment on PYRAMAX blood levels, hepatic impairment may alter the potential efficacy/toxicity of the combination.

There were no patients with severe renal or hepatic impairment in clinical studies and no specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. However, most patients with acute malaria present with some degree of related hepatic and/or renal impairment.

In clinical studies, the adverse event profile did not differ in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. Similarly, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function.

[redacted]

No specific dose adjustments are recommended for patients with mild to moderate renal impairment.

Underlying hepatic injury or significant liver function test abnormalities as well as severe renal impairment are contraindications in the current SmPC.

8 Patients with cardiac impairment

Patients were excluded if they had significant cardiac problems, so it is unknown what the effect of PYRAMAX on these patients is likely to be. However, apart from some bradycardia which may be related in part to the settling of tachycardia due to the resolution of fever with treatment, no cardiac events have been of significance. Therefore, it is not anticipated that the 3-day course of PYRAMAX would adversely affect patients with cardiac co-morbidity.

9 Patients of different ethnic origin

The Phase I study with repeat dose SP-C-014-11 was associated with a number of significant rises in transaminases in healthy Caucasian volunteers. It seems that the high observed frequency is more linked to the non-infected status of healthy volunteers than to the potential difference of metabolic pathways between ethnic origins.

The Phase II/III studies, the longitudinal study - SP-C-013-11, and the most recent cohort study - SP-C-021-15, were exclusively recruiting in people of African, Indian and Asian origin. There have been no significant racial differences with regard to efficacy or safety. Given the overwhelming predominance of African, Indian and Asian ethnic groups who are infected with malaria these will be the dominant groups where PYRAMAX will be prescribed.

10 Patients with Relevant Co-Morbidity

a) Anaemia

In the Phase II studies, there was no limit set on haemoglobin and, as a result, 7/477 (1.5%) patients in the adult study and 1/60 (1.7%) patients in the paediatric study were admitted with an Hb of <8 g/dL. On one occasion the further fall in haemoglobin which is commonly seen in the treatment of malaria led to a serious adverse event of heart failure. In the longitudinal study SP-C-013-11, the cut-off for haemoglobin was <7 g/dL and therefore experience was gained in this marginally lower range population.

The Phase IIIb/IV cohort (SP-C-021-15) study recruited patients without any exclusion criterion for lower haemoglobin level. Of the 7154 patients completing the study, 440, (6.2%) had a relevant medical history and concurrent illnesses on entry related to anaemia. Patient often present with anaemia due to malaria and if this is already low, the treatment of malaria usually causes a further fall which may result in anaemia being sufficient to cause symptoms or precipitate heart failure. There were no material or clinically significant trends identified for haematological parameters, regardless of LFT status at entry. Changes in mean haematological parameters from baseline did occur but these were consistent across patients with normal or abnormal LFTs at entry and generally returned to baseline or close to baseline levels by Day 28. The majority of haematological abnormalities resolved after malaria infection had been treated and reflected an anticipated host response to the infection. In the small number of patients with at least one available post-baseline assessment of haemoglobin, the mean haemoglobin level was observed to decrease on Day 7 compared to the established baseline. Recovery of mean haemoglobin levels to close to baseline levels was observed by Day 28. This trend was consistent regardless of patient LFT status at entry.

b) Patients with Human Immunodeficiency Virus

Patients with a known history of HIV were actively excluded from the **Phase I – III** studies although this condition frequently co-exists in patients with malaria and represents a treatment challenge.

[redacted]

c) Known active Hepatitis A IgM (HAV-IgM), Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody (HCV Ab)

Patients with known hepatitis or hepatitis antibodies were excluded the former as alternative active disease would confound the results of the study and the latter as a precaution for staff handling blood supplies. While the effects of PYRAMAX are not known in these patients there is no plausible reason why its efficacy or safety should be a concern in these patients except where liver failure is an issue and it would be expected that the patients would have signs and symptoms of liver disease and if this was compounded by the malaria then jaundice may be obvious; a contribution to this may also be the haemolysis of malaria that manifest as a raised bilirubin prior to treatment. Given the prevalence of co-infection as outlined in Section SI.2.1.5 it is possible that patients, who were not routinely tested for co-infection, may have had underlying disease or viral hepatitis. However, if this was the case and even if it contributed to the rises in transaminases in some instances, the pattern of rise and fall and the speed at which liver enzymes return to normal without treatment or sequelae suggests that the risk to patients with asymptomatic liver disease of the short course of PYRAMAX treatment is low. Patients with signs and/or symptoms of liver disease or those who are taking potentially hepatotoxic medication should be monitored as they are at greater risk than the population as a whole.

[redacted]

d) Sub-populations carrying known and relevant polymorphisms

G6PD deficiency was assessed proactively in study SP-C-006-06 and there did not appear to be an issue with safety of treatment in such patients compared to the rest of the population. Patients with haemoglobinopathies were not excluded from the studies except where this might have led to an Hb <8 g/dL and, in the overall Phase II/III study database, made up a very small proportion of patients overall.

[redacted]

There will continue to be no exclusion of these patients from future studies and information as it becomes available will be assessed to see if they are at greater risk. Otherwise routine pharmacovigilance will check for co-morbidities and assess whether this is contributory.

No other subpopulations with specific polymorphisms have been identified at this time.

Conclusions on the populations not studied and other limitations of the clinical trial development programme

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

Type of special population	Exposure
[redacted]	[redacted]
[redacted]	[redacted]
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with severe malaria were excluded from the studies and while hyperparasitaemia associated with severe malaria may be defined as a parasite density of >200,000/µL (WHO definition). [redacted]
[redacted]	[redacted]
Subpopulations carrying relevant genetic polymorphisms	G6PD deficiency was assessed proactively in study SP-C-006-06 and there did not appear to be an issue with safety of treatment in such patients compared to the rest of the population. Patients with haemoglobinopathies were not excluded from the studies except where this might have led to an Hb <8 g/dL and, in the overall Phase II/III study database, made up a very small proportion of

Type of special population	Exposure
	patients overall. [redacted] There will continue to be no exclusion of these patients from future studies and information as it becomes available will be assessed to see if they are at greater risk. No other subpopulations with specific polymorphisms have been identified at this time.
Malnourished children	Patients with severe malnutrition were excluded in the Phase I-III study programme. [redacted]
[redacted]	[redacted]

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Prescription data

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]
				[redacted]	[redacted]	[redacted]	[redacted]

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Neither pyronaridine nor artesunate are controlled drugs and do not represent a threat of abuse in the usual sense of the word. However, effective anti-malarial drugs are sought after and the potential for PYRAMAX to be illegally obtained and “prescribed” to prospective patients does pose a potential threat.

Misuse will be monitored in post-marketing use through special situation PV monitoring.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

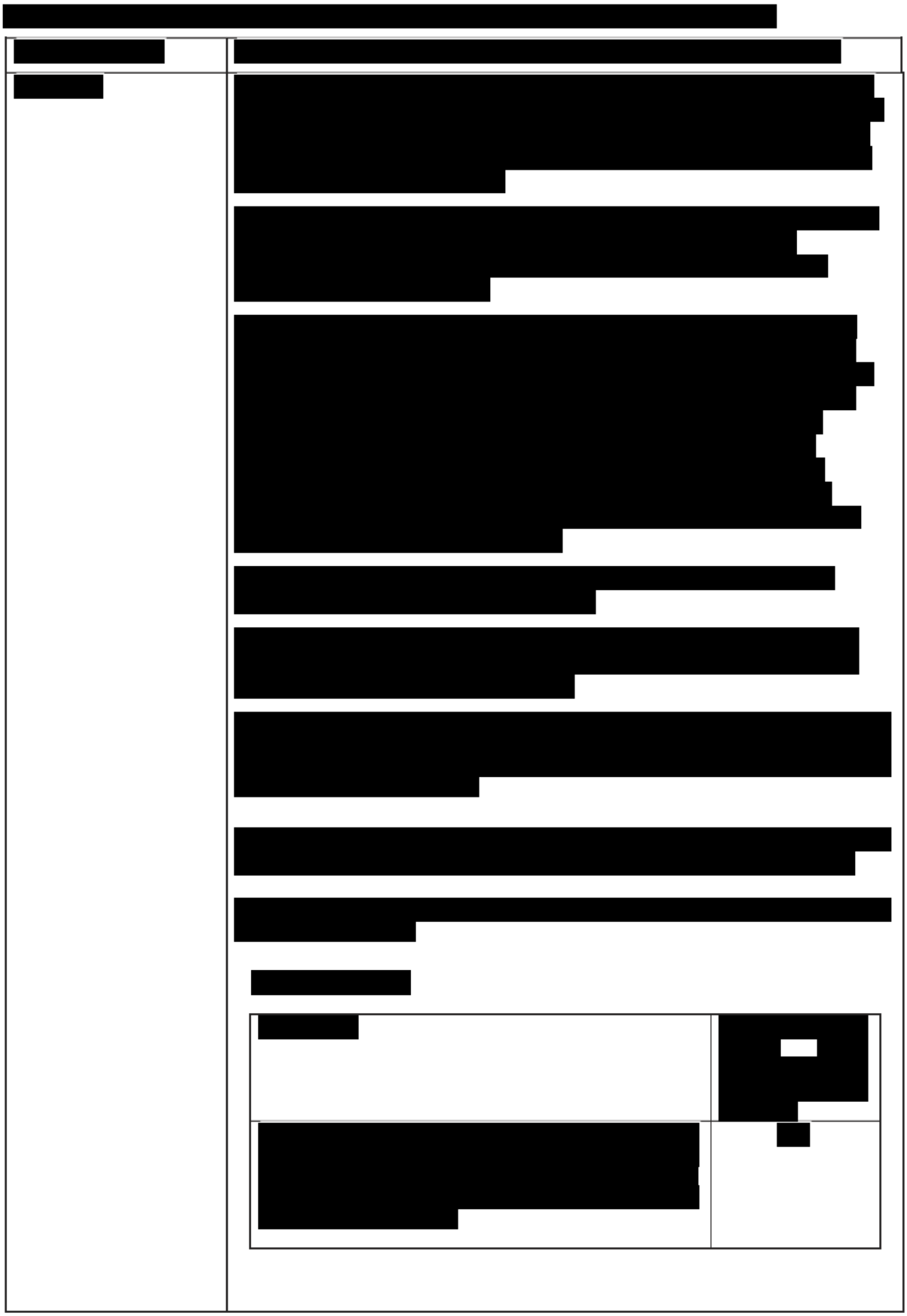
SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns have been identified**.** In Procedure No. EMEA/H/W/002319/II/0023/G, it was recommended to remove a number of safety concerns appropriately managed through routine pharmacovigilance, and without the need for additional pharmacovigilance activities or risk minimisation measures as reported in RMP Version 17.4 of important identified risks, important potential risks and missing information.

The following risks are retained in RMP Version 18 to be specifically monitored in the PSUR:

- Use in pregnancy and lactation - embryotoxicity/teratogenicity

[redacted]



Potential Risk 1	Use in pregnancy and lactation:- embryotoxicity/teratogenicity

Potential Risk 1	**Use in pregnancy and lactation:- embryotoxicity/teratogenicity**
Severity and nature of risk	Pyronaridine tetraphosphate caused maternal toxicity in pregnant rats and rabbits but was not teratogenic. Artesunate is, however, embryotoxic. There is, therefore, a potential risk of embryonic death particularly in the first trimester of pregnancy if PYRAMAX is taken during this time. It appears to be the artesunate component of PYRAMAX that is the issue. A meta-analysis of first-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia found that first-trimester use of artemisinin derivatives was not associated with an increased risk of miscarriage or stillbirth compared to quinine. The data to date also indicate no difference in the prevalence of major anomalies between treatment groups in early pregnancy (Dellicour 2017). A prospective cohort study of pregnant women conducted in Africa found no evidence of an increased risk of low birth weight, small for gestational age or prematurity among infants born to women with confirmed first-trimester exposure to an ACT (Augusto 2020). Further data have been acquired with the conduct of two sizable well-structured research projects which include PYRAMAX exposure in pregnant women. Both the MiMBa pregnancy registry and the PYRAPREG are conducted with well-established and respected research consortia who are highly experienced in studying the treatment of malaria in pregnant women. With both initiatives still ongoing the data are regarded as interim; however, the impact of the work has substantially improved the opportunity to examine how PYRAMAX exposure both treats the malaria infection and also provides the safety profile in both the mother and offspring. The endpoints and outcomes include those of malaria efficacy as well as pregnancy outcome and safety of PYRAMAX treatment in this population. The follow up of those babies born following exposure in these controlled settings will further provide reassurance in relation to any longer-term effects, as secondary or exploratory outputs.  The data collected to date on the use of PYRAMAX in pregnant women with uncomplicated malaria, with PYRAMAX can be considered to be encouraging and do not lead to an increase in adverse pregnancy outcomes, while these preliminary data also suggest that pregnancies losses are reduced by reducing the morbidity of untreated malaria. In a resetting of the guidance (2023) in relation to the treatment of uncomplicated malaria in pregnant women, World Health Organisation (WHO) have recently updated their guidance in relation to the treatment in pregnancy with artemisinin containing therapies. The redirection by WHO is predominantly based on a seminal paper authored by Saito et. al, 2023 entitled "Pregnancy outcomes after first-trimester treatment with artemisinin derivatives versus non-artemisinin antimalarials: a systematic review and individual patient data meta-analysis". The findings from the systematic review and meta-analysis were reflected in the WHO Guidelines for Malaria (16 October 2023).

Potential Risk 1	**Use in pregnancy and lactation:- embryotoxicity/teratogenicity**
	Until late 2022, WHO treatment guidelines recommended 7 days of quinine for treating uncomplicated *Plasmodium falciparum* malaria in the first trimester of pregnancy, despite its poor tolerability, compliance, and effectiveness. In 2017, a systematic literature review and meta-analysis assessed the safety of artemisinin derivatives in the first trimester of human pregnancies, showing no difference in the risk of miscarriage, stillbirth, and congenital anomalies between artemisinin-exposed and quinine-exposed pregnancies. In 2021, WHO sought to gather the evidence on the safety of antimalarials in the first trimester of pregnancy to establish whether ACTs could be reconsidered for the treatment of malaria in the first trimester. Resulting from the examination of a large dataset of cases for first trimester pregnancies, WHO has generated a new recommendation based on a review of all updated evidence to date on the risks and benefits of using any ACT compared to quinine for the treatment of uncomplicated *P. falciparum* malaria in the first trimester of pregnancy. The WHO guidance with regards to 2nd and 3rd trimesters pregnancy is that the artemisinin derivatives should be used to treat uncomplicated *P. falciparum* malaria in the second and third trimesters of pregnancy as there have been no adverse effects on the mother or foetus in large numbers of documented pregnancies. ACTs, particularly artemether-lumefantrine, have thus been the recommended first-line treatment in the second and third trimesters of pregnancy since 2006 and the extension of use to other ACTs has been made by WHO in the 2023 Guidance.
Background incidence/prevalence	While artemisinins are clearly embryotoxic in animals (White 2006, Clark 2009, Efferth 2010) it has not really been observed in human studies (Li 2010) where embryotoxicity has not been convincingly observed in clinical trials from 1,837 pregnant women, including 176 patients in the first trimester exposed to an artemisinin agent or artemisinin-based combination therapy (ACT) from 1989 to 2009. While malaria itself is associated with abortion and stillbirth, considered primarily to be a consequence of acute malaria illness more-recent studies of the role of malaria in abortion and stillbirth (including placental parasitisation and the host cell response) are lacking (Nosten 2004). As reported by Gore-Langton et al. (2020), globally in 2020, 120.4 million pregnancies were at risk of *P. falciparum*, two-thirds (81.0 million, 67.3%) were in areas of stable transmission while 85.2 million pregnancies were at risk of *P. vivax*. An estimated 64.6 million pregnancies were in areas with both *P. falciparum* and *P. vivax* transmission. The total number of pregnancies at risk of *P. falciparum* increased to 52.4 million in 2020. The adverse effects of *P. falciparum* are thought largely due to the sequestration of the parasite within the placenta and are particularly seen in women who have not been exposed to *P. falciparum* in any previous pregnancy. Malaria affects more than 25 million pregnant women every year, both in high and low malaria-endemic areas (WHO 2020). Malaria in pregnancy was associated with a 33% increase in pregnancy loss, and this increase can be as high as 60% in the first trimester. Malaria infection in the first trimester impairs placental vasculogenesis and angiogenesis as well as placental villous and vascular development, leading to gestational hypertension, maternal anaemia, low birth weight, foetal growth restriction, preterm birth, and pregnancy loss. Up to 200,000 infant deaths and 10,000 maternal deaths occur annually due to malaria in pregnancy (Desai et al., 2007). Maternal anaemia due to malaria is an independent risk factor for low birth weight and other impact factors on mother and baby. Malaria has been estimated to cause 24% of all low-birth-weight babies (WHO 2020). Low infant birth weight is the greatest single risk factor for death in the first month of life. In

Potential Risk 1	Use in pregnancy and lactation:- embryotoxicity/teratogenicity
	areas where malaria is endemic, 20-40% of all babies born may have a low birth weight. The risk of malaria infection is said to be highest in the first and second trimesters of pregnancy. Pregnant women constitute the main adult risk group for malaria and 80% of deaths due to malaria in Africa occur in pregnant women and children below the age of 5 years. Malaria is more common in pregnancy compared to the general population and malaria tends to be more atypical in presentation. This could be due to the hormonal, immunological and haematological changes of pregnancy with parasitaemia tending to be 10 times higher and as a result, all the complications of *P. falciparum* malaria are more common in pregnancy compared to the non-pregnant population. *P. falciparum* malaria in pregnancy is reported as more severe, with the mortality is also double compared to the non-pregnant population.
Risk groups or risk factors	There is a potential risk of embryonic death based on pre-clinical data; however, the risk of untreated malaria infection particularly in the first trimester of pregnancy is unacceptably high. The emerging data from all sources have shown that, not only is there no greater risk to the pregnancy or the foetus by treating the malaria with ACTs, but in fact there is a significant reduction in all of the complication of pregnancy including foetal loss, stillbirths, malformation and low birth weights. Therefore, the main risk group for complications of pregnancy in malaria are untreated pregnant patients. [redacted]
Potential mechanisms	Transient depletion of the primitive erythroblasts (White 2006) which may potentially show as a reduction in reticulocytes in pregnant women (Clark 2009). Other potential mechanisms are described above.
Preventability	While the administration of any medications during pregnancy should to be done with caution and contraception is still desirable, the emerging data suggest that there is no increased risk from treating with PYRAMAX versus other ACTs in any trimester of pregnancy and the risk of pregnancy complications is best prevented by the prompt treatment of malaria. Given the half-life of pyronaridine, patients should be encouraged not to breast feed within the first 90 days after receiving PYRAMAX.
Potential public health impact of safety concern	None apparent
Evidence source	[redacted]
MedDRA terms	N/A

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important potential risks	**Important potential risk 1:** Use in pregnancy and lactation - Embryotoxicity/teratogenicity

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

III.1.1. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

Shin Poong Pharmaceuticals has established an EU compliant pharmacovigilance (PV) system and, in parallel with the national regulatory submission, is establishing the full organisation of post-marketing pharmacovigilance in countries where PYRAMAX is to be marketed. The currently established systems are already in use for collection, review and assessment of adverse events for any ongoing clinical trials. This includes a compliant expedited regulatory reporting system to cover all countries where clinical studies are run.

Prior to product authorisation in each country, Shin Poong Pharmaceuticals have in place arrangements with either their Affiliates or distributor and all pharmacovigilance obligations will be wholly met by these parties. All such agreements will be specified in contracts between the parties and the Competent Authorities as appropriate and the EMA will be informed of any revisions to the Pharmacovigilance System Master File (PSMF) prior to placing the product on the market in any country. Post-marketing pharmacovigilance procedures will be performed according to SOPs for handling post-marketing pharmacovigilance related activities which are either in place or will be in place well in advance of placing the product on the market.

In terms of adverse event collection:

- The PV system applies the principles of the WHO guidance document (A practical handbook on the pharmacovigilance of antimalarial medicines Published by the WHO 2007) and Guidelines on Good Pharmacovigilance Practices 2016, 2017.
- The PYRAMAX PV system reports to EMA through the established process of PSURs, the first PSUR having been submitted to EMA September 2012.
- The spontaneous reporting of any safety issues associated with PYRAMAX will be encouraged including adverse event reports and reports of special situations.
- All adverse events will first be received by the local distributor company in each country, and these will then be forwarded to the SOH who in turn will forward them to the global PV supplier as outlined in the PSMF.

- [redacted]
- Analysis of all safety data is undertaken on an ongoing basis through the PV partner of Shin Poong and is discussed on a regular basis at the Quarterly Safely Review by Shin Poong and EU QPPV as outlined in the PSMF.

III.1.2. Specific adverse reaction follow-up questionnaires for safety concerns:

There are currently no specific follow up questionnaires used to collect post authorisation safety data.

III.1.3. Other forms of routine pharmacovigilance activities for safety concerns:

Not Applicable.

III.1.4. Routine Pharmacovigilance activities in Malaria Endemic countries.

Almost all regulatory authorities in malaria endemic countries have regulations for pharmacovigilance but it varies from country to country as to how it is being implemented and the systems maintained. Many countries have reporting forms where an address/fax number of a local recipient organisation is stated representing the local regulatory authority; but the level of implementation of such systems is part of a public campaign at a low level and sufficient training or national monitoring systems are not well established yet. WHO has guidelines for the target standard of pharmacovigilance system in malaria endemic countries. Shin Poong works with the National Malaria Programmes in the respective countries and is aligned to the pharmacovigilance programmes.

[redacted]

III.2 Additional pharmacovigilance activities

A registry to document pregnancy data arising from commercial or trial use of PYRAMAX has been established (SP-PV-001-12) which is reported to EMA on a 3 yearly cycle. The SP-PV-001-12 Pyramax Pregnancy Registry is a Category 3 post-authorisation safety study (PASS) activity.

PASS Pregnancy Registry Summary:

SP-PV-001-12 PYRAMAX Pregnancy Registry: Assessment of the Safety of PYRAMAX Use During Pregnancy
Rationale and Study Objectives:
The objective of the study is to monitor all pregnancies and their outcomes in women receiving PYRAMAX for the treatment of uncomplicated malaria

Study design:

This is an open reporting of cases where women who receive PYRAMAX for treatment of uncomplicated malaria are reported to be pregnant.

Study population:

Females prescribed PYRAMAX for the treatment of uncomplicated malaria.

Milestones:

Study ongoing and reported at regular intervals to EMA.

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1. Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Potential Risks	
Use in pregnant and lactating women – risk of embryotoxicity/teratogenicity	Routine risk communication: SmPC section 4.4; 4.6 and PL. The presence of a pregnancy registry is highlighted in the SmPC. In section 5.3 of the SmPC data is provided on reproductive toxicity. For lactation: SmPC section 4.6 and PL. For fertility: SmPC section 4.6 also provides further preclinical information in fertility and reproduction.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of PYRAMAX.

V.3. Summary of risk minimisation measures

Table Part V.2. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Proposed risk minimisation activities	Proposed pharmacovigilance activities
Embryotoxicity/teratogenicity	Routine risk minimisation measures: Information in sections 4.4, 4.6 and 5.3 of the SmPC	[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for PYRAMAX (Pyronaridine tetraphosphate/Artesunate)

This is a summary of the risk management plan (RMP) for PYRAMAX. The RMP details important risks of PYRAMAX, how these risks can be minimised, and how more information will be obtained about PYRAMAX's risks and uncertainties (missing information).

PYRAMAX's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how PYRAMAX should be used.

Important new concerns or changes to the current ones will be included in updates of PYRAMAX RMP.

I. The medicine and what it is used for

PYRAMAX Tablets are authorised for the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in adults and children weighing 20 kg or more.

PYRAMAX granules for oral suspension are authorised for the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in children and infants weighing 5 kg to under 20 kg (see SmPC for the full indication). It contains pyronaridine tetraphosphate and artesunate as the active substance and it is given by mouth.

Further information about the evaluation of PYRAMAX's benefits can be found in PYRAMAX's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/pyramax-h-w-2319.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of PYRAMAX, together with measures to minimise such risks and the proposed studies for learning more about PYRAMAX 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of PYRAMAX is not yet available, it is listed under 'missing information' below.

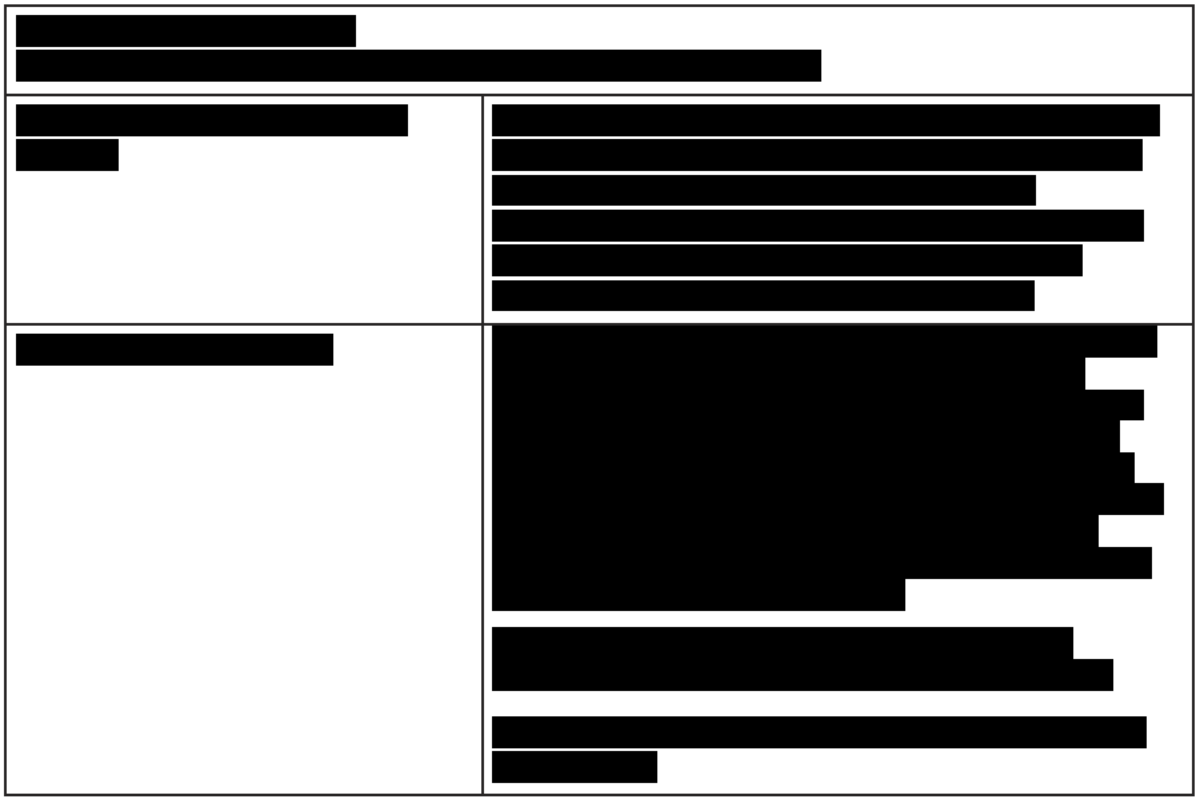
II.A List of important risks and missing information

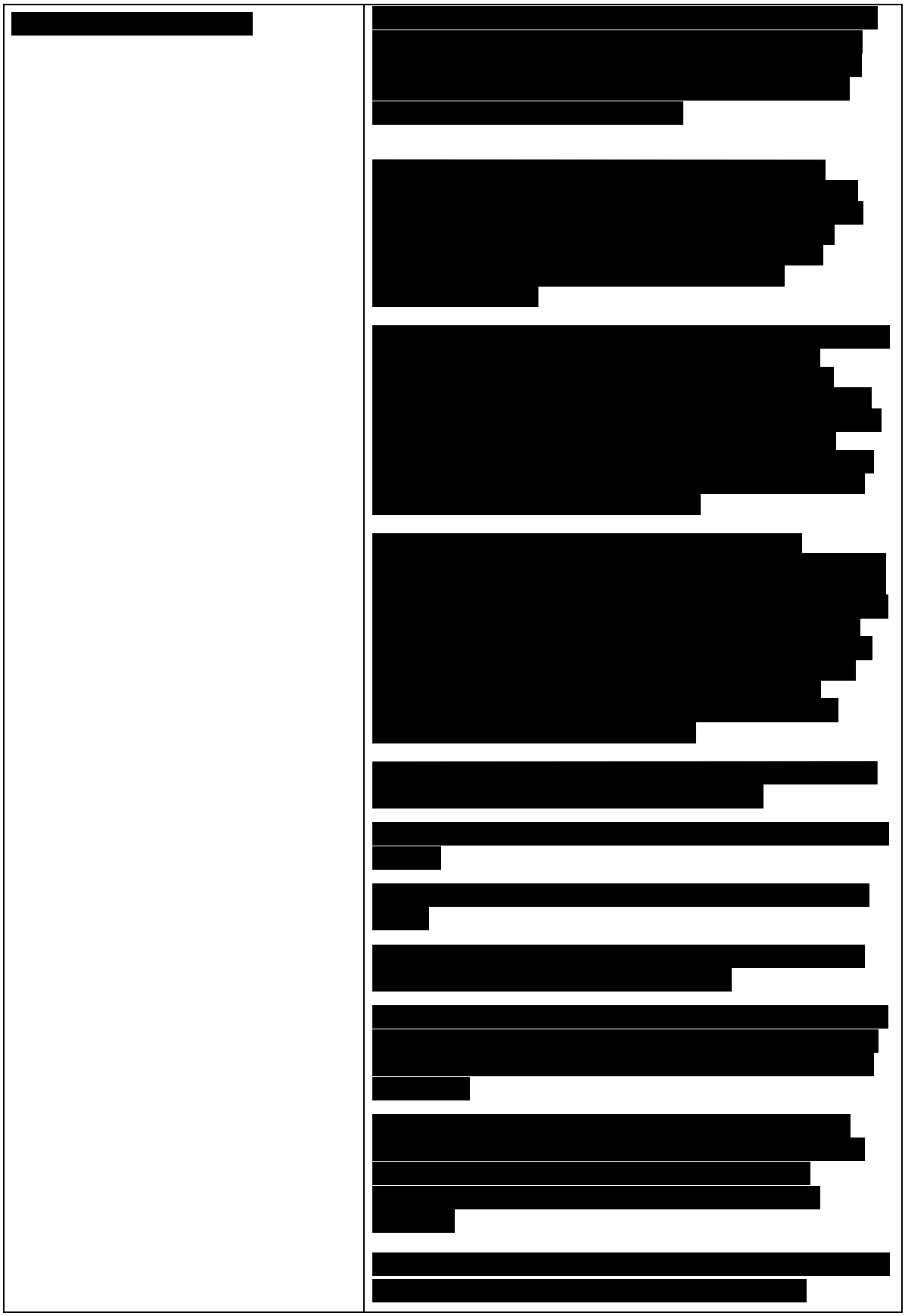
Important risks of PYRAMAX are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PYRAMAX. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the types of patients who might receive the medicine).

Summary of safety concerns	
Important potential risks	Use in pregnancy and lactation • Embryotoxicity/teratogenicity

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.





[redacted]	[redacted]

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no further studies which are conditions of the marketing authorisation or specific obligation of PYRAMAX.

II.C.2 Other studies in post-authorisation development plan

SP-PV-001-12 Pregnancy Registry

Monitor all pregnancies and their outcomes. Monitor use in pregnant and lactating women – including risk of embryotoxicity/ teratogenicity

Ongoing

3 year reporting cycle

Annexes

[redacted]

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1. Annex 2 Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
SP-PV-001-12 Pyramax Pregnancy Registry; Assessment of the Safety of Pyramax Use During Pregnancy Category 3	to capture the cases of pregnancy in women who have received Pyramax during the conduct of a clinical trial or via prescription who conceive up to 8 weeks post administration or exposure to Pyramax in women who are already pregnant (healthy volunteers and malaria patients), in order to track progress of the pregnancy and outcome.	**Incidence of normal births, abnormal outcomes (e.g., abortions) and the health of the new-born infant (up to 4 weeks following birth)**	**This is a live, ongoing registry**

[redacted]

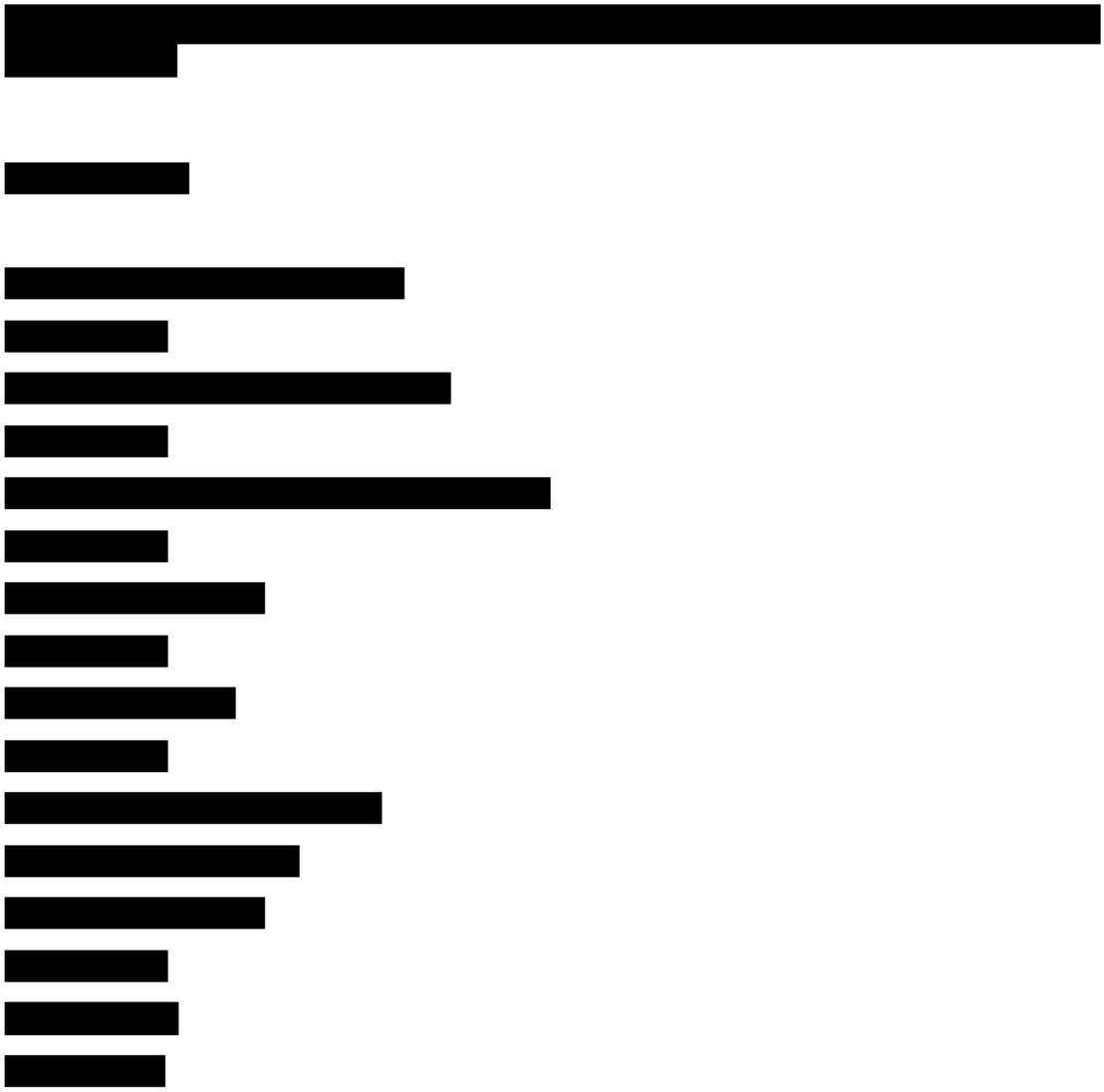
Table 2. Annex 2 [redacted]

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

Not Applicable

[redacted]



[redacted]

[redacted]	[redacted]	[redacted]
		[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]