20 July 2017
EMA/103576/2018
Committee for Medicinal Products for Human use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Eurartesim

International non-proprietary name: piperaquine tetraphosphate/ artenimol/ dihydroartemisinin

Procedure No. EMEA/H/C/001199/P46/016

Note

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

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Introduction

Eurartesim is an anti-malarial agent for the treatment of uncomplicated Plasmodium falciparum malaria in adults, children and infants 6 months and over and weighing 5 kg or more. The approved Eurartesim formulation is a conventional fixed combination immediate release film-coated tablet containing Piperaquine Tetraphosphate (PQP) and Dihydroartemisinin (DHA) as drug substances in the strength combinations 320mg/40mg and 160mg/20mg intended for adult (adult presentation) and children between 5 and 25 kg (paediatric presentation), respectively.

Since small children are not able to swallow tablets, a commitment was undertaken by the Applicant to develop a more suitable formulation for more easy and accurate drug administration in paediatric patients. The pharmaceutical and clinical development of a paediatric formulation has been discussed and approved by the PDCO within a PIP procedure (EMEA-000153-PIP01-07).

At the time of the approval of Eurartesim (October 2011), the PIP was not finalized yet; therefore, the completion of the paediatric plan was included in the list of post-approval obligations reported in the Risk Management Plan.

Originally, the study proposed in the approved PIP was an open-label study to evaluate pharmacokinetic, safety and efficacy of two strength oral dispersible tablets (80/10 and 160/20 mg PQP/DHA), in 200 paediatric patients aged 6-12 months with uncomplicated P. falciparum malaria. According to the commitment undertaken within the RMP, the protocol synopsis for the clinical study, already approved by the PDCO, was submitted to the CHMP in April 2012.

The Assessment Report received from CHMP in August 2012 included the following comment:

'The formulation to be used in this study is different to the one approved. Since the applicant proposes to replace the film-coated tablets with the dispersible tablets in this age group, it is not clear how these formulations will be compared to justify the PK characteristics and dosing schedule. If aiming to bridge to the original clinical studies, an additional group taking the conventional film-coated tablet would be expected. The applicant should justify the lack of such a group and demonstrate how this issue will be addressed.'

Following this request, the MAH modified the study design by adding a group of 100 children taking the conventional treatment (crushed film coated tablets) and introducing a PK/PD analysis aiming to bridge to the original clinical studies carried out with the film-coated tablets in paediatric population.

A request for modification of the approved PIP was then submitted to include the changes strongly recommended by the CHMP as well as postponement of the timelines for completion of the study. The RfM of the PIP was finally approved in August 2016 with the commitment to submit the study report to the CHMP and the PDCO as soon as finalised.

The approved study is coded ST3073-ST3074-DM12002 and titled "A phase II, open-label, multicentre, pharmacokinetic, pharmacodynamics and safety study of a new paediatric Eurartesim dispersible formulation and crushed film coated Eurartesim tablet, in infant patients with Plasmodium falciparum malaria".

The study started on November 2013, the in vivo phase was completed on 02 June 2015 (last patient out), the database freeze occurred on 11 December 2015, due to the complexity to retrieve all the study documents, filter papers and blood smear for central readings from African sites and finally to obtain the centralised readings. The bioanalytical report was issued on 12 November 2015, the statistical analytical report for efficacy and safety data was issued on 31 May 2016, the PK/PD analysis

report was issued on 8 November 2016, and finally the integrated clinical study report was issued on 27 January 2017.

On 3 February 2017, the MAH submitted a completed paediatric study for Eurartesim, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study ST3073-ST3074-DM-12-002 "a phase II, open-label, pharmacokinetic, pharmacodynamics and safety study of a new paediatric Eurartesim dispersible formulation and crushed film coated Eurartesim tablet, in infant patients with *Plasmodium falciparum* Malaria" is part of a clinical development program. The extension application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by December 2017. A line listing of all the concerned studies is annexed.

1.2. Information on the pharmaceutical formulation used in the study

Eurartesim new paediatric pharmaceutical Formulation

The new paediatric formulation used in this study is a water dispersible tablet. The pharmaceutical development of this formulation was conducted taking into consideration the chemical-physical properties of both APIs present in the fixed combination. In order to guarantee an acceptable palatability for children, the first step of the dispersible tablet development was to mask the bitter taste of piperaquine. This was achieved by microencapsulation of piperaquine particles and addition of a flavouring agent. The microencapsulation process consists in applying a thin polymeric coating material to the small particles in a uniform and reproducible way: ethylcellulose was used as the coating agent.

As a second step, the two active substances (PQP and DHA) were separated into two distinct layers to form a bilayer tablet, to avoid enhancing degradation of dihydroartemisinin due to the presence of water and phosphoric acid contained in PQP.

An industrial scale batch of the bilayer dispersible tablets has been used in this study.

CHMP comments:

No module 3 has been provided with the current submission. The applicant should clarify whether this has been previously submitted and assessed. Information on CMC, qualitative and quantitative composition, manufacturing process as well as in-vitro dissolution results needs to be provided.

The MAH should also clarify if both strengths of the dispersible formulation were produced at the industrial batch size. The batch size for each of the formulations should be presented.

1.3. Clinical aspects

1.3.1. Introduction

- The MAH submitted a final report for:Study ST3073-ST3074-DM-12-002 “a phase II, open-label, pharmacokinetic, pharmacodynamics and safety study of a new paediatric Eurartesim dispersible formulation and crushed film coated Eurartesim tablet, in infant patients with *Plasmodium falciparum* Malaria

1.3.2. Clinical study

Study No ST3073-ST3074-DM-12-002: A phase II, open-label, pharmacokinetic, pharmacodynamics and safety study of a new paediatric Eurartesim dispersible formulation and crushed film coated Eurartesim tablet, in infant patients with *Plasmodium falciparum* Malaria

Description

Study Title

A phase II, open-label, multicentre, pharmacokinetic, pharmacodynamics and safety study of a new paediatric Eurartesim dispersible formulation and crushed film coated Eurartesim tablet, in infant patients with Plasmodium falciparum malaria.

Methods

Study Design

The present study was a randomized open label study of 300 children (aged 6 to 12 months); a comparison between the approved tablet, crushed and administered with water, and the dispersible tablet was conducted in order to evaluate population pharmacokinetics, efficacy and safety parameters. It was multi-centre, with all centres in Africa. The first patient was enrolled on 12 November 2013 and the last patient completed on 02 June 2015.

The two arms were allocated with a ratio of 2:1 (dispersible vs crushed film coated formulations).

Study Objectives

Primary Objective: To assess the PK of the Eurartesim (PQP/DHA) new water dispersible formulation, film coated tablet and crushed film coated tablet in venous blood samples during and after a therapeutic course of Eurartesim in paediatric population.

Secondary Objectives:

- To evaluate the efficacy of Eurartesim in treating uncomplicated malaria episodes and its ability in protecting patients from reinfections and/or recrudescence.
- To assess the PK/PD relationship of Eurartesim in malaria patients.
- To evaluate safety and tolerability of Eurartesim in infants.

Methodology

A seven-sites phase II, randomised, open label, two-arm parallel group study. Three-hundred sub-Saharan African (from 6 to ≤ 12 months of age) infants visiting the study clinics and for whom a

diagnosis of uncomplicated P. falciparum malaria (according to the WHO criteria) had to be confirmed by a microscopic parasitological diagnosis and quantitative parasitaemia, and whose parents or guardians signed informed consent were included in the study. Two hundred children had to be treated with Eurartesim dispersible tablet formulations (strength according to body weight), while one hundred children had to be treated with crushed film-coated tablet. An allocation ratio of 2:1 (dispersible versus crushed film coated formulation) was applied. Data coming from the group administered with the crushed film coated formulation had to be utilised to strengthen the population pharmacokinetic model built up on data coming from the film coated formulation. Dispersible tablets or crushed film-coated tablets were administered for three days (study Days 0, 1 and 2) under supervision. Follow-up visits on study Days 7, 14, 21, 28 and 42 were conducted as out-patients.

Inclusion / Exclusion criteria

Inclusion criteria:

- Male and Female infants aged from 6 months to ≤ 12 months included.
- Ability to swallow oral suspension.
- Body weight ≥5 kg.
- Uncomplicated malaria, with microscopically confirmed mono-infection by P. falciparum (parasitaemia ≥1000/µL and <200000/µL).
- History of fever anytime during the preceding 48 hours or presence of fever (axillary temperature ≥37.5 °C or ≥38.0 °C rectally).
- Ability of parents or guardians to understand the nature of the trial and providing signed informed consent.
- Stable residence in the study area during the two months after recruitment and willingness to comply with the study protocol and the study visit schedule.

Main Exclusion Criteria:

- Antimalarial treatment with amodiaquine, chloroquine, quinine or lumefantrine-based compounds within the previous 6 weeks, with piperaquine-based compound, or mefloquine, or sulphadoxine pyrimethamine (SP) within the previous 3 months and with halofantrine within the 30 days prior to screening.
- Any other antimalarial treatment or antibiotics with antimalarial activity (including cotrimoxazol) and any herbal products, within the 7 days prior to screening.
- Severe malnutrition (defined as weight for height <70% of the median NCHS/WHO reference).
- Severe vomiting or dehydration.
- Presence of jaundice.
- Known hypersensitivity to the artemisinin-based therapy or piperaquine.

Criteria for Evaluation

Pharmacokinetic: venous blood samples to determine DHA and PQ plasma concentration during and after Eurartesim therapy.

Efficacy: Thick and thin blood smears to verify the presence of P. falciparum and to calculate the asexual and sexual parasite density. PCR to genotype P. falciparum.

Safety: Haematology & biochemistry, ECG, vital signs, patient symptoms & physical examination, adverse events (AEs).

Study population

The analysis populations were as follows:

PK population: The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.

ITT population: The Intention-to-Treat (ITT) population included all patients taking at least one dose of the study drug. This population has been used for the Efficacy and Safety analysis. As for the Safety data presentation, it has been referenced as Safety Population.

PP population: The Per Protocol (PP) population included all patients who took the complete treatment and who did not meet any major protocol violations. The PP population has been used for the Efficacy analysis and the PK/PD analysis.

Dose justification

Each patient received a specific amount of drug according to his/her body weight once a day for three consecutive days.

Body weight (kg)	Daily dose (mg)	Number of tablets per dose	
		Dispersible tablets	Film Coated Crushed Tablet
5 to < 7	80 mg PQP and 10 mg DHA	1 tablet (80 PQP/10 DHA mg)	½ tablet (160 mg PQP/20 mg DHA)
7 to < 13	160 mg PQP and 20 mg DHA	1 tablet (160 mg PQP/20 mg DHA)	1 tablet (160 mg PQP/20 mg DHA)
13 to < 24	320 mg PQP and 40 mg DHA	2 tablets (160 mg PQP/20 mg DHA)	2 tablets (160 mg PQP/20 mg DHA)

The daily dose was to be re-administered in case of vomiting within 30 minutes from the drug administration, while half dose was re-administered in case of vomiting occurring between 30 and 60 minutes after the drug administration. In case of repeated vomiting the drug was not be re-administered more than once and another drug for malaria treatment (rescue treatment) was adopted.

Formulations used

The new Paediatric eurartesim dispersible tablet formulation was provided in two different strengths: 80/10 or 160/20 mg piperaquine tetraphosphate (PQP)/dihydroartemisinin (DHA) while the film coated tablet was a 160/20 mg piperaquine tetraphosphate (PQP) /dihydroartemisinin (DHA) formulation.

Due to possible food interaction, the first dose of eurartesim was administered as soon as the patient was randomized in the study and preferably no food was administered in the following three hours. For the second and the third drug administration the child was to be fed three hours before the scheduled drug intake. Those infants still requiring breast feeding received only maternal milk.

Concomitant Treatments

No other investigational drugs were allowed during the study.

Rescue treatments

Patients with treatment failure were to be treated and followed up as per local guidelines for malaria treatment till full recovery.

Study procedures

All the children from Day 0 (the day of the first study drug intake) to Day 3 remained admitted at the study clinic under supervision. Blood samples were collected over 72 h and then on Days 7, 14 and 21, according to the sparse blood sampling collections.

Pharmacokinetic assessments:

In order to minimize the blood sampling in infants, patients were randomly divided into 10 blood sampling groups for both treatments (water dispersible and crushed film coated tablet) and only 2 blood draws (1,5 mL each) per group were taken. The pharmacokinetic assessment was performed using analysis population PK approach because of the sparse sampling.

Based on previous clinical PK data, optimal sampling design was performed by using the appropriate software (e.g.ADAPT5, WinPOPT, PFIM, etc.). The D-optimal design option was used to determine the optimal sampling design.

The blood sampling time scheme presented for both DHA and PQ were not exactly the ones that were minimizing the objective function because some of them were below the quantitation limit, others were rounded to comply with the outpatient study visits.

Blood sampling for PK analysis of DHA in plasma collected as follows:

Day	0*						
Time (hh:mm)	00:20	00:30	00:40	01:00	01:40	03:20	05:00
DHA	Gr1	Gr2	Gr3	Gr4	Gr5	Gr6	Gr7

Blood sampling for PK analysis of PQ in plasma will be collected as follows:

Day	0*				1**	2***				3***	7***	14***	21***
Time (hh:mm)	00:40	01:20	04:40	12:00	24:00	00:40	01:20	04:40	12:00	24:00	120:00	288:00	456:00
PQ	Gr8	Gr9	Gr10	Gr1	Gr2	Gr3	Gr4	Gr5	Gr6	Gr7	Gr8	Gr9	Gr10

* Time calculated from the first dose; ** pre second dose (time calculated from first dose); ***Time calculated from the third dose.

Safety and Tolerability

- Blood samples collected for Haematology, biochemistry (BUN, Glucose, Creatinine, ALT/AST, Total Bilirubine, electrolytes (Na+, K+ and Cl)
- ECGs (triplicate readings) on Day 0 (at screening), single ECG on D2 (i.e. before the last drug administration) as well as triplicate ECG on Day 2 (i.e. 4 - 6 hours after the last drug administration).
- Treatment Emergent Adverse Events recording collected at Day 0, Day 1, Day 2, Day 3, Day 7, Day 14 (±1), Day 21 (-1), Day 28 (±3) and Day 42

Efficacy assessments

- Day 28 PCR-corrected Adequate Clinical and Parasitological Response (ACPR).
- Day 28 Crude (PCR-uncorrected) ACPR.

- Evaluation of patient's early and late Treatment Failure (TF).
- Asexual parasite density and clearance time (PCT)
- Fever clearance time (FCT).
- Gametocyte carriage and density over time.
- Day 42 ACPR (PCR corrected and PCR uncorrected).
- Kaplan Maier survival analysis for all recurrences over time.
- Kaplan Maier survival analysis for new infections over time.
- Kaplan Maier survival analysis for recrudescence over time.
- Malaria blood smear (thick and thin blood films)

Sample size:

The sample size for the target population PK study was estimated on the basis of the previous PK study in which 10 children per group for a total of 3 groups of blood sampling (5 blood samples per children per group) were included. Due to blood sampling limit of two blood samples per child, ten groups of 30 children each (20 children receiving the dispersible formulation and 10 children receiving the crushed film coated tablets in accordance to a 2:1 ratio of dispersible vs crushed formulations) were necessary to define the DHA and PQ PK profiles, according to a very sparse sampling scheme.

Results

Subject Disposition and Baseline Characteristics:

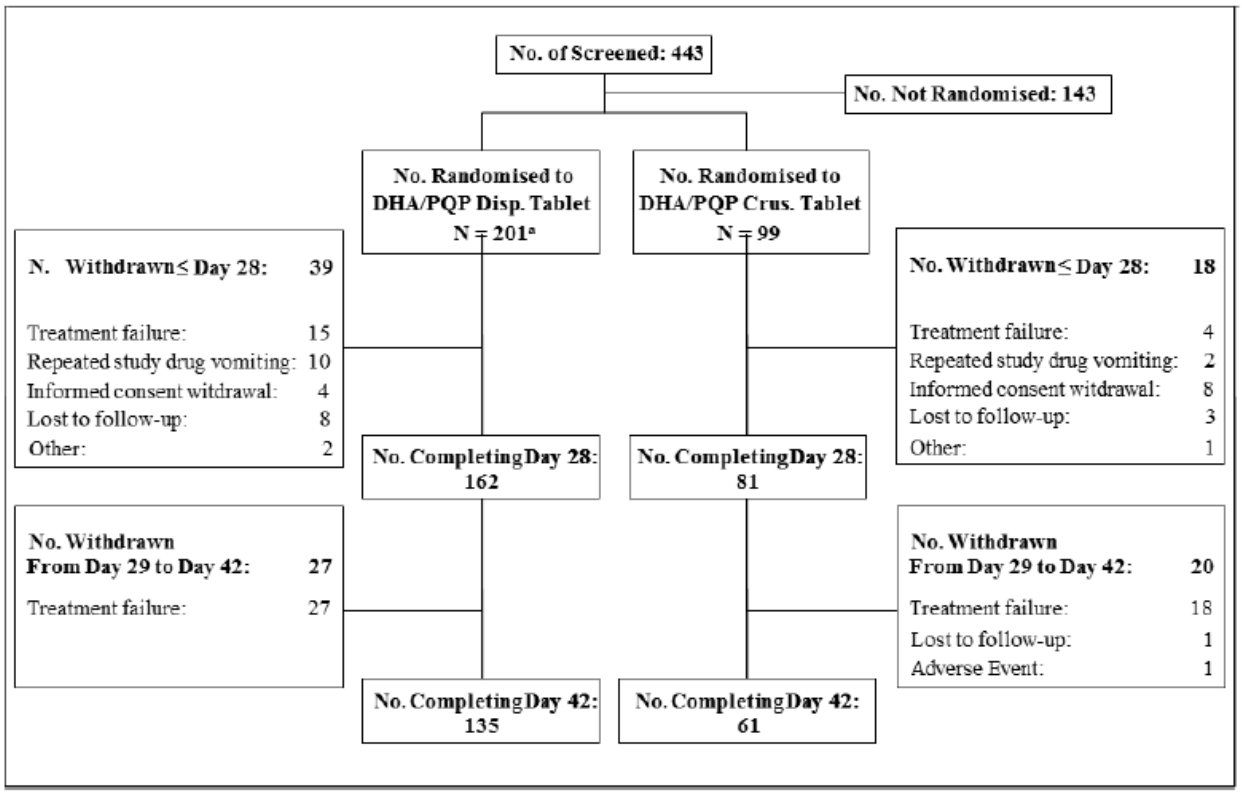


Table 10.1-1: Patient Accountability by Country (Safety/Pure ITT Population)

Group	PQP/DHA Dispersible Tablet				PQP/DHA Crushed Tablet			
Study Population	Safety/ITT (199)		PP (173)		Safety/ITT (99)		PP (84)	
	n	%	n	%	n	%	n	%
Total	199	100	173	100	99	100	84	100
Mozambique	90	45.22	83	47.97	51	51.52	40	47.62
Gambia	11	5.53	6	3.47	3	3.03	3	3.57
Congo	26	13.07	25	14.45	7	7.07	7	8.33
Burkina Faso	67	33.67	57	32.95	37	37.37	33	39.29
Tanzania	5	2.51	2	1.16	1	1.01	1	1.19

Mozambique: site 1; The Gambia: site 2; DR Congo: site 3; Burkina Faso: site 4 and site5; Tanzania: site 6 and site 7

Protocol Violations

Table 10.2-1: Summary of Major Violations in All Randomised Patients

Treatment Group	PQP/DHA Dispersible Tablet						PQP/DHA Crushed Tablet		
Site	01	02	03	04	05	06	01	04	05
Total number patients by site	92	11	26	38	29	4	51	21	16
Total number patients with violations	9	5	1	5	5	3	11	2	2
% of patients with violations	9.8	45.5	3.8	13.2	17.2	75.0	21.6	9.5	12.5
Major Protocol Violation									
Assigned treatment not taken	1*	0	0	0	0	0	0	0	0
Randomized with negative parasitaemia	1	0	0	0	0	0	0	0	0
Repeated study drug vomiting	0	3	0	4	3	0	0	1	1
Study drug uncompliance	0	0	0	0	1	1	0	0	0
Presence of jaundice at screening	0	1	0	0	0	0	0	0	0
Consent withdrawal	1*	1	0	0	0	2	6	1	1
Visit Day 28 not performed and malaria recurrence at Day 42	1	0	0	0	0	0	1	0	0
Lost-to-follow-up at or before Day 42	6	0	1	1	0	0	3	0	0
Move out to different area	0	0	0	0	1	0	0	0	0
Leave the hospital without informing study staff	0	0	0	0	0	0	1	0	0

* Violations occurring in the same patient.

Demographic Characteristics

Table 12.2.1-1: Demographic Characteristics (All populations)

Demographic Characteristics	PQP/DHA Dispersible Tablet		PQP/DHA Crushed Tablet	
	Safety/ ITT	PP	Safety/ ITT	PP
n	199	173	99	84
Male	89 (44.72%)	77 (44.51%)	47 (47.47%)	39 (46.43%)
Female	110 (55.28%)	96 (55.49%)	52 (52.53%)	45 (53.57%)
Mean Age (Months)	9.1	9.2	9.2	9.1
Median Age (Months)	9.0	9.0	9.0	9.0
Age Range (Months)	6-12	6-12	6-12	6-12
Black	199 (100%)	173 (100%)	99 (100%)	84 (100%)
Mean Weight (kg)	7.9	7.9	8.0	7.9
Median Weight (kg)	7.7	7.8	7.9	7.9
Weight Range (kg)	5.1-11.9	5.1-11.9	5.5-11.2	5.5-10.7

Source: Table 14.2.1 n = number of patients

Subjects were generally in balance across the groups. Physical examination findings showed that lung abnormalities were reported as the most frequent abnormalities (33% in the PQP/DHA dispersible formulation group, 23% in the PQP/DHA crushed formulation group) followed by abdomen (14% in both groups), ears, nose and throat (9% in the PQP/DHA dispersible formulation group, 5% in the PQP/DHA crushed formulation group) and skin abnormalities (7% in the PQP/DHA dispersible formulation group, 5% in the PQP/DHA crushed formulation group). Nearly half of all patients had fever reported as other findings in the physical examination. Most of these clinical features were consistent with acute malaria.

Antipyretic drugs were the most frequent previous medications: 15% and 7% of patients in the PQP/DHA dispersible and PQP/DHA crushed formulation groups, respectively, received paracetamol. Antipyretic and antiinfective agents were the most frequent concomitant medications. In addition, patients experiencing malaria recurrences were treated with antimalarial drugs.

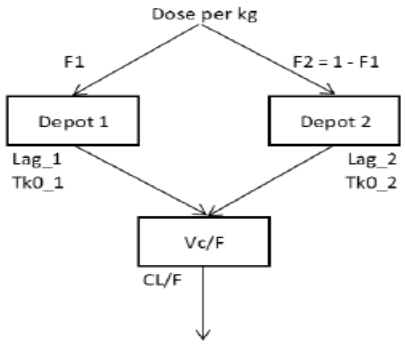
Treatment compliance was ensured by the study nurse or investigator supervising dose administration and observing patients for one hour after dosing. A patient was compliant with treatment if 100% of study medication was taken. Patients who vomited after first treatment intake but did not vomit again after re-dosing were counted as having assumed the treatment as scheduled. Patients who vomited after re-dosing or experienced an ETF before the third dose (in the first two days of treatment) were categorised as not taking the required percentage of treatment.

One-hundred eighty-nine (189) patients (95.0%) in the PQP/DHA dispersible formulation group and 95 patients (96.0%) in the PQP/DHA crushed formulation group were compliant to study treatment for ITT population, while for the PP population, the compliers were 172 (99.4%) in the PQP/DHA dispersible formulation group and 84 (100.0%) in the DHA/ PQP crushed formulation group. The only patient experiencing an ETF after the first drug intake (because of signs of severe malaria) and not having reached 100% compliance was included in the PP population although the 100% compliance was requested as criterion for inclusion; in fact, the patient reached a clinical endpoint. This decision was taken to maintain a conservative approach for the analysis of efficacy.

PK AND PK/PD RESULTS:

DHA population PK modelling: The final model for DHA was a 1- compartment PK model with 2 zero order absorption processes and 2 lag times.

DHA Structural Model



F1(2) = Proportion of the absorbed dose that is related to the first (second) zero order, Lag_1(2) = Absorption Lag Time of the first (second) zero order absorption, Tk0_1 (2) = Duration of the first (second) zero order absorption, Vc/F = Apparent Volume of the central compartment, CL/F = Apparent Clearance from the central compartment.

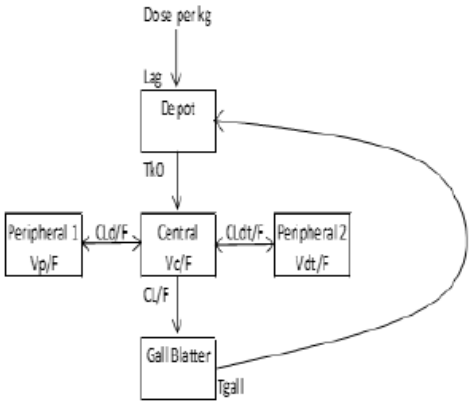
DHA Final Model Population Estimates

Parameter	Estimate	%RSE
FrelPAT	2.53	7.03
FrelFORM	0.731	4.55
Alpha	0.475	6.48
Alpha_PAT	0.936	8.95
Lag_1(h)	0.326	4.13
Lag_1_CRSH	0.496	28.2
Lag_1_FORM	0.716	15.1
Tk0_1(h)	0.471	8.43
Tk0_1_FORM	0.841	15.1
Tk0_1_FED	1.89	9.70
Tk0_1_CHILD	0.786	14.4
Lag_2(h)	0.672	7.99
Lag_2_FED	1.22	8.71
Tk0_2(h)	1.43	8.66
Tk0_2_FED	1.53	9.19
CL/F(L/h/kg)	3.08	2.59
Vc/F(L/kg)	4.30	2.89
SDslope	0.260	2.02
SDinter	4.31	9.35

F1 = Alpha/(Alpha + 1), %RSE = Percent of relative standard error their corresponding Maximum Likelihood Estimates, Variance of DHA concentration = $(SDslope*Y(1) + SDinter)^2$, where Y(1) is the predicted DHA concentration from the model.

PQ population PK modelling: The final model for PQ in plasma was a 3-compartment PK model with a lag time, and zero order absorption. The figure below presents the PK model for PQ. Enterohepatic recycling was fitted by adding an additional lag time for the emptying of the gallbladder with a dose equal to the amount of drug excreted since last gallbladder emptying.

PQ Structural Model



F1(2) = Proportion of the absorbed dose that is related to the first (second) zero order, Lag_1(2) = Absorption Lag Time of the first (second) zero order absorption, Tk0_1 (2) = Duration of the first (second) zero order absorption, Vc/F = Apparent Volume of the central compartment, CL/F = Apparent Clearance from the central compartment.

PQ Final Model Population Estimates

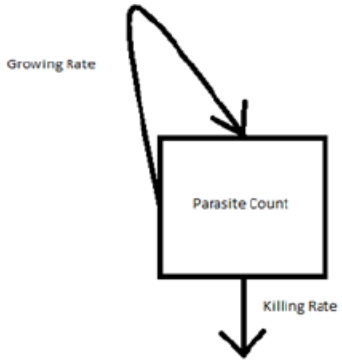
Parameter	Estimate	%RSE
FrelPAT	0.588	5.09
Lag (h)	0.769	2.79
LagFED	1.19	3.16
LagCRSH	0.291	12.9
LagFORM	0.443	5.74
Tk0 (h)	2.88	5.27
Tk0CRSH	0.749	12.8
Tk0PAT	1.31	6.41
CL/F(L/h/kg)	0.845	6.50
CL_PAT	0.720	7.72
Vc/F (L/kg)	25.2	6.60
CLd/F (L/h/kg)	3.80	6.06
Vp/F (L/kg)	43.6	5.62
CLdt/F (L/h/kg)	1.34	5.86
CLdtSEX	0.762	7.72
Vdt/F (L/kg)	464	6.50
Tgall (h)	1.52	4.73
FrelFED	1.79	5.24
FrelFED_CRSH	0.622	8.20
FrelFED_FORM	0.501	6.85
F_OCC1	0.806	4.00
SDslope	0.322	0.952

%RSE = Percent of their corresponding Maximum Likelihood Estimates, Variance of PQ concentration = $(SDslope*Y(1) + SDinter)^2$, where Y(1) is the predicted PQ concentration from the model, and SDinter was fixed to 0.01.

PK/ PD modelling: The final PK/PD model was a 1-compartment model with a parasite growing rate, and killing rate as a function of DHA and PQ concentration. The figure below presents the model for parasite count as a function of DHA and PQ cincentrations. An Onset of effect parameter was used to model the delay between the appearance of DHA and PQ in plasma and the killing effect of the drug. DHA killing rate was modeled with an Emax function and the PQ killing rate was modeled with a

sigmoidal Emax function. Antagonism between the effects of DHA and PQ incorporated into the model. A mixture model with two groups was included in the model for the parameter DHAmax since it had a bimodal distribution probably due to a different parasite population with different resistance to the effect of DHA. It was estimated that approximately 57% of the parasite population developed some resistance to the effect of DHA.

Parasiete Count Structural Model



PQ Final Model Population Estimates

Parameter	Estimate	%RSE
Kgrow (1/h)	0.0604	1.25
DHAmax_Low (1/h)	0.534	4.83
DHAmax_High (1/h)	1.36	6.49
DHA50 (ng/mL)	0.267	33.1
PQmax (1/h)	0.234	8.79
PQ50 (ng/mL)	9.40	12.5
HillPQ	15.3	15.2
Onset (h)	8.02	5.68
SDslope	0.193	2.57
SDinter	-0.0408	10.5

%RSE = Percent of their corresponding Maximum Likelihood Estimates, Variance of PQ concentration = $(|SDslope| \times Ypred + |SDinter|)^2$, where Ypred is the predicted LOG(Parasite Count +2) from the model.

The DHA PK model predicted that Frel was higher in patients than in healthy volunteers, (253%). The Frel was also influenced by the formulation being lower for the water dispersible formulation compared to the old formulation (73%).

The first zero order adsorption process accounted for the absorption of about 31-32% of DHA dose. The lag time associated with the first zero order was approximately 19.6 and 14 minutes for the old and new formulation, respectively, and decreased to 9.7 minutes when the old formulation was crushed.

The duration of the first zero order adsorption (Tk0_1) process for a typical child under fed condition increased to 42 and 35.3 minutes for the old and new formulation, respectively compared to adult (22.2 and 18.7 minutes, for the old and new formulation, respectively). Either in adults or in children TK¬01 was slower under fed condition.

The DHA model predicted that the second zero order adsorption process (Tk0_2) was influenced only by food, being slower when Eurartesim was administered under fed condition (1 h 26 min and 2 h 11 min under fasting and fed condition respectively). CL/F and Vc/F were not influenced by any covariate; they were typically 3.08 L/h/kg and 4.30 L/kg, respectively. The residual variability of DHA model was 28.8%.

The PQ PK model predicted that Frel was lower in patients than in healthy volunteers, (58.8%). Frel for the first PQ dose was 80.6% compared to the subsequent PQ doses. Only under fed condition, PQ Frel was influenced by the formulation, being 179, 111 and 89.7% with the film coated tablet, the crushed film coated tablet and the water dispersible formulation, respectively.

The PQ PK model predicted that lag time associated with the zero order process was longer with the film coated tablet (46 min) compared to the crushed tabled (13 min) or the water dispersible formulation (20 min). In addition, PQ lag time was influenced by the food.

The PQ duration of the zero order adsorption (Tk0) process was longer in patients that in healthy volunteers (2.9 h vs 3.8 h), for both Tk0 was shorter with crushed tablet (2.2 and 2.9 h in healthy volunteers and patients, respectively). The formulation did not influenced the Tk0 duration.

By the model, the PQ CL/F was predicted higher in healthy subjects than in patients (0.845 L/h/kg vs 0.608 L/h/kg). Furthermore, the apparent distributional clearance between the central and peripheral 2 compartments (CLdt/F) was influenced by the sex being lower for female than male (1.02 vs 1.34 L/h/kg).

All the other PK parameters for PQ were not influenced by any covariate. they were typically 3.08 L/h/kg and 4.30 L/kg, respectively. The typical value for Vc/F, CLd/F, Vp/F, and Vdt/F were 25.2 L/kg, 3.80 L/h/kg, 43.6 L/kg, and 464 L/kg, respectively. The Tgall emptying for a typical subject was estimated to be approximate 1.5 hour after the lag time. The residual variability of this model was 32.2%.

A PK/PD model was developed to describe the parasite count as a function of the PK of PQ and DHA plasma concentration. The PK/PD model predicted in vivo IC50 for DHA and PQ similar to those reported in literature from in vitro studies (0.267 and 9.4ng/mL for DHA and PQ respectively). The model estimated two DHA MIC: 0.0124 and 0.0340 ng/mL for a typical patient with non-resistant and resistant parasite population, respectively, it was estimated that approximately 57% of the parasite population developed some resistance to the effect of DHA. Conversely, the DHA MPC was the same for both the parasite population (26.4ng/mL). The MIC and MPC estimated for PQ were 8.77 and 12.7ng/mL, respectively.

Aiming to compare the PK and PK/PD profiles for crushed film coated and water dispersible formulations, simulations were carried out on 200 male and female virtual paediatric patients aging between 6 and 12 months involved in a 2-way crossover design study with the two treatments.

MICs and MPCs

The typical inhibition concentrations that give 50% of the maximum effect (IC50) from the PD model were close to the in vitro IC50 reported in the literature. The reported in vitro IC50 range for DHA is 0.9 nM to 2.6 nM (0.256 ng/mL to 0.739 ng/mL) and the estimated in vivo DHA IC50 for a typical patient was 0.267 ng/mL, which is within the range reported in the literature. It should be noted that the %RSE for DHA50 was 33.1% which was the largest %RSE for the typical value in patients. It was probably due to the fact that the LOQ for DHA was much higher in these studies with a value of 10 ng/mL compared to DHA50 (2.267 ng/mL). The in vivo PQ50 for a typical patient was 9.40 ng/mL, which was close to the range reported for the in vitro IC50 for PQ, which ranged between 25.1 nM to 49.7 nM (13.4 ng/mL to 26.6 ng/mL).

The MIC was the concentration that results in a parasite killing rate equal to the parasite growth rate, i.e. no parasite growth. The minimum parasiticidal concentration (MPC) was the concentration that results in at least 99% of the maximum killing rate for the drug, i.e. a concentration with the maximum effect of the medication.

Table 11.6.1-1: MIC and MPC for a Typical African Patient

Parameter	DHA (ng/mL)	PQ (ng/mL)
MIC	0.0124	8.77
MPC	26.4	12.7

The comparison between the old crushed and the new formulation for a typical paediatric patient weighing 8 kg are presented. The below figures depict the two formulations for a typical patient with and without resistance to the effect of DHA. The maximum concentration was higher for the old crushed formulation compared to the new formulation for both DHA and PQ. However, the differences

in PD response for the two formulations were comparable. Both formulations exhibited an onset of effect approximately 8 hours following the first dose and rapidly reached a killing rate close to DHAmax at approximately 8.4 hours postdose. Both formulations reached high steady killing rates for duration of approximately 4 to 5 hours and then declined down to a killing rate of 0.234 1/h by approximately 23 hours after the first dose for the new formulation and 0.4 hour later for the old formulation. Then both formulations' killing rates were steady at the maximum killing rate of PQ until the effect of the second dose took place.

Figure 11.6.1-3: Comparison between the Old and New Formulation

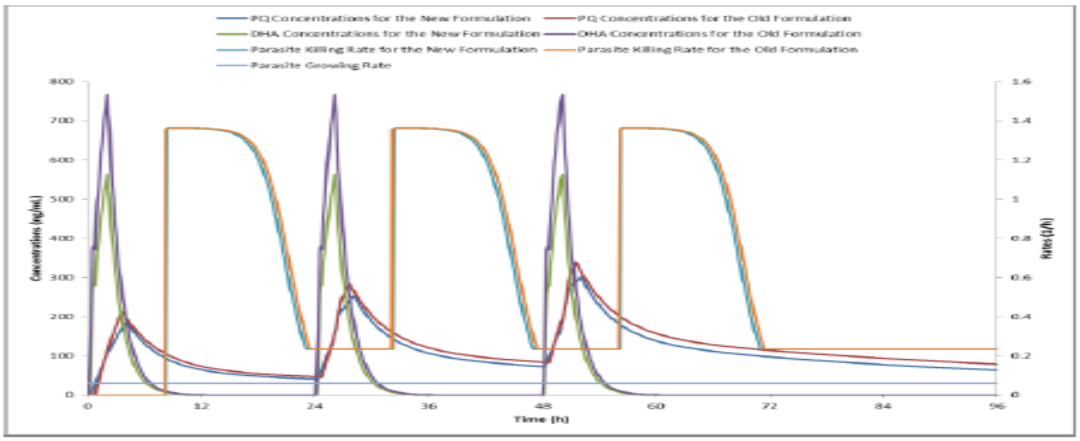
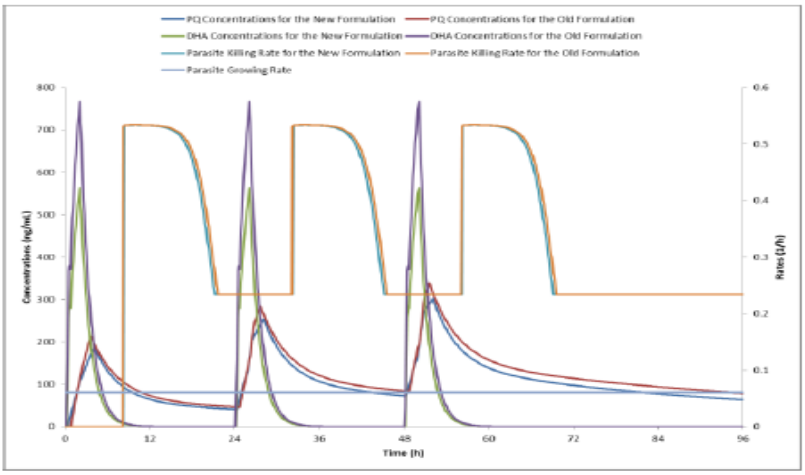


Figure 11.6.1-4: Comparison Between the Old and New Formulation with Parasite Population Resistant to the Effect of DHA



Simulated Population

Aiming to compare the PK and PD profiles of Eurartesim dispersible (new) and crushed (old) formulations, Pop PK and PK/PD final model parameters were used to simulate patient's PK and PD profiles. A 2-way crossover design study with two treatments (old crushed and new formulation) was used.

Two hundred (200) virtual paediatric patients, aged between 6 and 12 months infected with malaria were created. The paediatric population was simulated according to the following order: sex, age (assumed uniformly distributed), body weight (according to the formulas from the WHO in the Training Course on Child Growth Assessment, and Eurartesim dose.

The simulated population consisted of 113 male and 87 female paediatric patients having frequency of the age and body weight (descriptive summary) as presented in Table 11.6.2-1 and Table 11.6.2-2

Table 11.6.2-1: Frequency of the Simulated Age

Age (month)	6	7	8	9	10	11	12
Frequency (n)	27	38	31	24	25	30	25

n = number of patients

Table 11.6.2-2: Summary of the Simulated Body Weight

Descriptive stat.	min	1st Quartile	Median	Mean	3rd Quartile	Max
Body weight (kg)	5.186	7.741	8.586	8.630	9.480	11.950

The dose administered in the simulation followed the dosing regimen in the Study ST3073/ST3074-DM-12-002. If the body weight was less than 7 kg, then the patient was receiving 80/10 mg PQP/DHA. If the body weight was greater or equal to 7 kg and less than 13 kg, then the patient received 160/20 mg PQP/DHA, and if the body weight was greater or equal to 13 kg, then the patient received 320/40 mg PQP/DHA.

Bioequivalence

PQ and DHA concentrations were simulated with a concentration at every 0.1 hours between 0 and 24 hour. The PK parameters Cmax, area under the curve up to the last measurable concentration (AUClast) and area under the curve extrapolated to infinity (AUCinf) were evaluated using the simulated concentrations between 0 and 24 hour for PQ and 0 to 12 hour for DHA. The simulated concentrations at the beginning of the profile that were BLQ were set to zero and those after the first measurable concentration were set to missing. The apparent elimination rate constant (Kel) was estimated with all the data points following but not including Cmax. If the slope used to evaluate the Kel was positive, AUCinf was set to missing. AUClast was calculated by using the linear-trapezoidal method.

Mean, median, 5th and 95th percentile of the DHA and PQ simulated concentrations for each formulation are presented below.

Figure 11.6.3-1: Mean, Median, 5th and 95th Percentile of the DHA Simulated Concentrations for Each Formulation

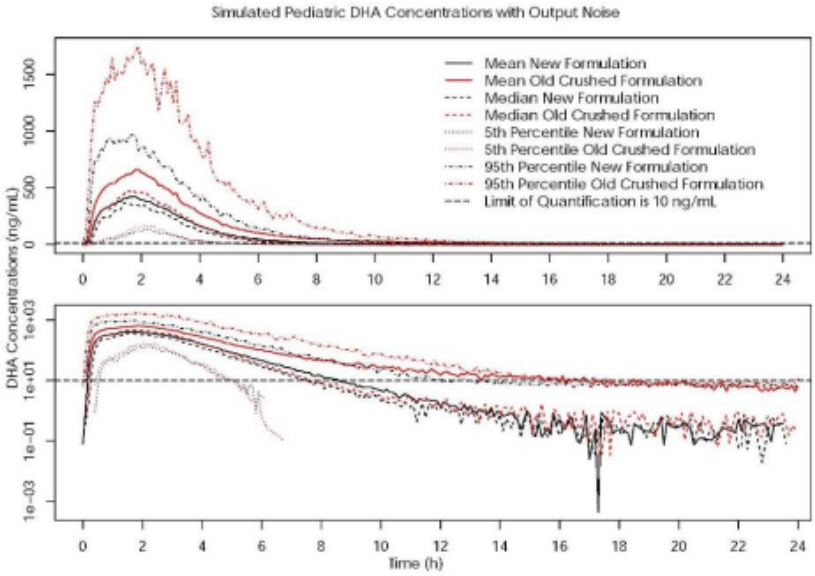
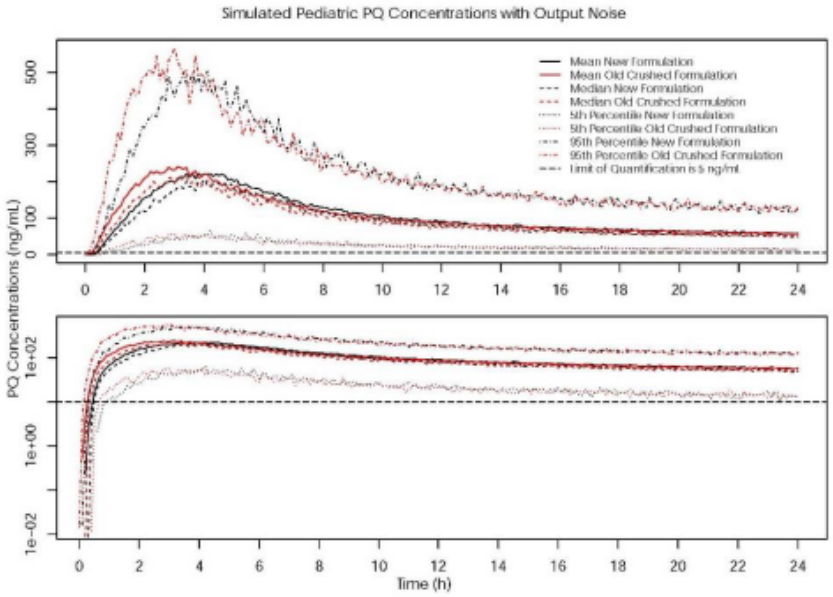


Figure 11.6.3-2: Mean, Median, 5th and 95th Percentile of the PQ Simulated Concentrations for Each Formulation



The geometric mean ratios (GMR), lower and upper 90%CI for bioequivalence assessment and the geometric CV% for Cmax, AUClast and AUCinf obtained from the simulation of the two formulations in 200 paediatric male and female patients are presented Table 11.6.3-1. The point estimate for the bioequivalence ratios of the new dispersible formulation over the old crushed formulation were within the 80-125% acceptance range for PQ but not for DHA, as expected from Pop PK analyses since the ratios from the PQ and DHA models were 100% and 73.1%, respectively. The geometric CV% for the

new formulation were generally lower than for the old formulation, suggesting a lower inter-individual variability, as expected for an age-appropriate formulation.

Table 11.6.3-1: Geometric Mean Ratios (GMRs), Lower and Upper 90% CI and Geometric CV% of the New and Old Formulations for DHA and PQ Cmax, AUClast and AUCinf

Parameter	New/Old GMR (%)	Lower 90% CI	Upper 90% CI	New Formulation Geometric CV (%)	Old Formulation Geometric CV (%)
DHA Cmax	71.6	64.9%	79.0%	69.1	76.2
DHA AUClast	70.0	63.5%	77.2%	67.8	77.5
DHA AUCinf	69.9	63.3%	77.2%	67.6	78.3
PQ Cmax	93.7	84.7%	103.8%	72.8	74.1
PQ AUClast	98.6	90.1%	108.0%	70.6	70.7
PQ AUCinf	93.5	83.3%	104.9%	73.8	81.1

Time above MIC (TMIC) and Time above MPC (TMPC)

As already described the MIC is drug concentration that inhibits the parasite growing rate; while the MPC is the drug concentration with the maximum effect of the medication, therefore the time above MIC (TMIC) and time above MPC (TMPC) are the time interval during which a patient is exposed to effective drug concentrations.

The TMIC and TMPC were calculated following the PK simulation and the descriptive statistics are presented Table 11.6.4-1. The mean TMPC and TMIC for PQ for both formulations were approximatively the same at 23 hours. The old crushed formulation remained on average approximately 1 and 0.5 hours longer above the MPC and MIC for DHA compared to the new formulation, respectively.

Table 11.6.4-1: Descriptive Statistic for the Estimated TMPC and TMIC for PQ and DHA Concentrations Estimated Between 0 and 24 Hours

Parameter	Formulation	Minimum	1st Quartile	Median	Mean	3rd Quartile	Maximum
PQ TMPC (h)	New	4.3	23.2	23.4	23.0	23.5	23.8
PQ TMPC (h)	Old crushed	4.8	23.4	23.6	23.2	23.7	23.9
PQ TMIC (h)	New	7.9	23.3	23.5	23.3	23.6	23.9
PQ TMIC (h)	Old crushed	8.0	23.5	23.7	23.5	23.7	24.0
DHA TMPC (h)	New	3.4	4.9	5.7	6.0	6.8	13.2
DHA TMPC(h)	Old crushed	2.8	5.1	6.1	7.0	7.9	23.9

Time to Parasite Clearance

The 200 simulated virtual PK patients were used with the final parasite count model to simulate the parasite count without output noise for a typical paediatric patient. Prior to simulating the Parasite Count, a binomial distribution with parameters size = 1 and prob = 0.4285593 was used to determine if the parasite was resistant to the effect of DHA for each patient. Seventy-three (73) out of the 200 simulated patients had malaria parasite sensitive to the effect of DHA. Also the initial parasite counts were simulated (the same within patient for each treatment). A transformation of the initial parasite count was used to have a distribution close to a normal distribution. The transformation of the data at

an exponent of 1/3 was used. If a simulated initial parasite count was outside the measured parasite count, it was re-simulated until a value within the observed range was obtained.

The summary statistics for the first time that the parasite count decreased below 0.5 are presented in Table 11.6.5-1 for the new and old crushed formulations. On average, both treatments require approximately 34 hours before the parasite count reached zero. The CVs for the new and old crushed formulations were 35.7 % and 35.9%, respectively. The individual plots for these typical patients without output noise are presented in Section 16.4.2.

The same 200 virtual patients in the 2-way crossover used for the simulations for the PK were used for the simulations of the parasite count. For each profile 200 simulations were performed and the mean of the LOG(parasite count + 2) was used. Table 11.6.5-2 presents the descriptive statistics. On average the new formulation reached a parasite count level below 0.5 for the first time approximatively 1 hour faster when compared to the old crushed formulation. The CVs for the new and old crushed formulations were 39.3% and 37.6%, respectively. The plots for the mean, median, 5th and 95th percentile of the simulated parasite count for both formulations can be found in Figure 11.6.5-1.

Table 11.6.5-1: Descriptive Statistics for the Time to Parasite Clearance from a Typical African PatientDecreased Below 0.5 parasites/µL

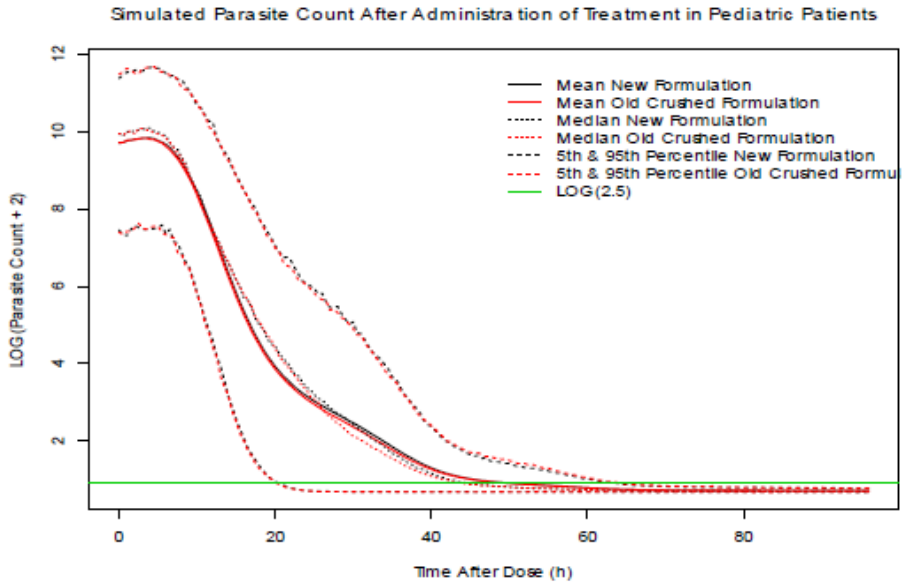
Formulation	Minimum	1st Quartile	Median	Mean	3rd Quartile	Maximum
New	15.38	19.38	39.33	34.13	43.42	58.78
Old Crushed	15.13	19.35	37.83	33.70	42.77	58.90

Table 11.6.5-2: Descriptive Statistics for the Time to Parasite Clearance for 200 Simulated Parasite Count with Output Noise Patients Decreased Below 0.5 parasites/µL

Formulation	Minimum	1st Quartile	Median	Mean	3rd Quartile	Maximum
New	18.5	22.5	44.5	41.5	56.5	71.5
Old Crushed*	19.5	24.0	46.0	42.8	56.5	71.0

* One of the simulated patients did not reach a parasite count below 0.5

Figure 11.6.5-1: Mean, Median, 5th and 95th of the 200 Simulated Parasite Count with Output Noise for both Formulations



PHARMACOKINETIC AND PK/PD CONCLUSIONS

The primary objective of this study was to assess the PK of Eurartesim (PQP/DHA) in a new water dispersible formulation, film coated tablet, and crushed film coated tablet in venous blood samples during and after a therapeutic course of Eurartesim in a paediatric population. The primary endpoint was to estimate the population and individual PK parameters and variability of PQ and DHA in paediatric populations administered with Eurartesim.

The final model for DHA was a 1-compartment PK model with two zero-order absorption processes each with a lag time. The covariates included in the final model were FORM and PAT on the relative bioavailability, PAT on Alpha (parameter used to calculate proportion of the absorbed drug for the first and second absorption process), CRSH and FORM on Lag_1, CHILD, FED and FORM on Tk0_1, and FED on Lag_2 and Tk0_2.

The final model for PQ was a 3-compartment PK model with a zero-order absorption process and a lag time. Enterohepatic recycling was fitted by adding an additional lag time for the emptying of the gallbladder with a dose equal to the amount of drug excreted since the last gallbladder emptying. The covariates included in the final model were FED and PAT on the relative bioavailability, CRSH and FORM on FrelFED, FED, CRSH, and FORM on Lag, CRCH and PAT on Tk0, PAT on CL/F, and SEX on CLdt/F.

One of the secondary objectives of the study was to assess the PK/PD relationship of Eurartesim in malaria patients (adult and paediatric populations). The objective was to obtain a comprehensive PK/PD relationship for DHA and PQ after administration of Eurartesim as a film coated tablet, crushed film coated tablet, or water dispersible tablet in malaria patients. Modeling of P. falciparum parasite density was performed and the effect of covariates on the PD modeling was explored.

A PK/PD model was developed to describe the parasite count as a function of the PK of PQ and DHA plasma concentration. The model was a 1-compartment model with a parasite growing rate, and killing rate as a function of DHA and PQ concentration. An Onset of effect parameter was used to model the delay between the appearance of DHA and PQ in plasma and the killing effect of the drug. DHA killing rate was modeled with an Emax function and the PQ killing rate was modeled with a sigmoidal Emax function. Antagonism between the effects of DHA and PQ incorporated into the model by taking the parasite killing rate to be the maximum between the killing rate of DHA and PQ. The initial conditions (value in the compartment at time zero) were fixed to the measured parasite count and the fitted Y was equal to LOG(parasite count + 2). The structure of the variance-covariance matrix was diagonal. A mixture model with two groups was included in the model for the parameter DHAmax since it had a bimodal distribution probably due to a different parasite population with different resistance to the effect of DHA. It was estimated that approximately 57% of the parasite population developed some resistance to the effect of DHA.

The PK for PQ was bioequivalent between the new water dispersible formulation and crushed film coated tablet. Conversely, the PK for DHA was not bioequivalent between the new water dispersible formulation and crushed film coated tablet, however, the effects between the two treatments were comparable.

The applicant states that the simulations confirmed that the PK for PQ but not for DHA was bioequivalent between the new water dispersible formulation and crushed film coated tablet. The mean PQ TMPC was about 23 h for both the formulations while the mean DHA TMPC differed of about 1 h between the formulations. Finally, the simulated time to parasite clearances differed for about 1 h between the Eurartesim crushed film coated tablet and the water dispersible formulations, indicating that the effects between the two treatments were comparable.

Summary of Efficacy Results

Summary of Results for PCR-Uncorrected and Corrected ACPR at Day 28 and Day 42 (All Populations)

Endpoint		PCR-Uncorrected ACPR		PCR-Corrected ACPR	
Study Population	Day	PQP/DHA Dispersible Tablet	PQP/DHA Crushed Tablet	PQP/DHA Dispersible Tablet	PQP/DHA Crushed Tablet
ITT	28	80.9%	80.8%	86.9%	84.9%
	42	67.8%	61.6%	85.9%	82.8%
PP	28	91.3%	95.2%	98.3%	100%
	42	76.3%	72.6%	96.5%	96.4%

At Day 28, in both treatment groups, uncorrected ACPR was very similar in the ITT population (80.9% and 80.8% for the dispersible and crushed formulations, respectively). In the PP population, uncorrected ACPR were 91.3% and 95.2% for the dispersible and crushed formulations, respectively. The two-sided 95% asymptotic CIs were: -0.094-0.096, Δ = 0.10% and -0.101-0.023, Δ = -3.9% for the ITT and PP populations, respectively.

At Day 28, in both treatment groups, corrected ACPR was similar in the ITT population (86.9% and 84.9% for the dispersible and crushed formulations, respectively. In the PP population, corrected ACPR were 98.3% and 100% for the dispersible and crushed formulations, respectively. The two-sided 95% asymptotic CIs were: -0.064-0.106, Δ = 2.1% and -0.037-0.002, Δ = -1.7% for the ITT and PP populations, respectively.

At Day 42 in the ITT population, corrected ACPR was 85.9% and 82.8% for the dispersible and crushed formulations, respectively. In the PP population, corrected ACPR were 96.5% and 96.4% for the dispersible and crushed formulations, respectively. The two-sided 95% asymptotic CIs were: -0.053-0.178, Δ = 62% and -0.078-0.151, Δ = 3.7% for the ITT and PP populations, respectively.

At Day 42 in the ITT population, uncorrected ACPR was 67.84% and 61.62% for the dispersible and crushed formulations, respectively. In the PP population, uncorrected ACPR were 76.30% and 72.62% for the dispersible and crushed formulations, respectively. The two-sided 95% asymptotic CIs were: -0.058-0.120, Δ = 3.1% and -0.047-0.049, Δ = 0.1% for the ITT and PP populations, respectively.

With respect to the PCR-Corrected/Uncorrected ACPR at Day 28 and at Day 42, the comparison between PQP/DHA dispersible formulation group and PQP/DHA crushed formulation group showed no clinically significant differences, considering overall the ITT and the PP populations (all the CIs contained the value 0).

The Day 28 PCR-Corrected ACPR obtained in this study were similar to those obtained in the previous Phase III trial conducted in African children, 90.4% and 95.7% in the ITT and PP populations respectively.

Summary of Results for Incidences of New Infection and Recrudescences at Day 28 and Day 42 (All Populations)

Endpoint		New *P. Falciparum* Infections		Recrudescence	
Study Population	Day	PQP/DHA Dispersible Tablet	PQP/DHA Crushed Tablet	PQP/DHA Dispersible Tablet	PQP/DHA Crushed Tablet
ITT	28	6.0% (12 out 199)	4.0% (4 out 99)	1.0% (2 out 199)	0% (0 out 99)
	42	18.1% (36 out 199)	21.2% (21 out 99)	2.5% (5 out 199)	1.0% (1 out 99)
PP	28	6.9% (12 out 173)	4.8% (4 out 84)	1.2% (2 out 173)	0% (0 out 84)
	42	20.2% (35 out 173)	23.8% (20 out 84)	2.3% (4 out 173)*	0% (0 out 84)*

* Two patients (one for each group) had a malaria recurrence. For both patients filter paper were not available and therefore no PCR was performed. DSMB decided to consider these patients as failure for the ITT and as missing for the PP population.

Within Day 28, and in the ITT population, the incidence of new P. falciparum infections documented by PCR analysis were 6% and 4% in the PQP/DHA dispersible and crushed formulation groups, respectively. The incidence of recrudescences documented by PCR analysis were 1.0% and 0% in the PQP/DHA dispersible and crushed formulation groups, respectively.

Within Day 42, and in the ITT population, the incidence of new P. falciparum infections were 18.1% and 21.2% in the PQP/DHA dispersible and crushed formulation groups, respectively. The incidence of recrudescence were 2.5% and 1.0% in the PQP/DHA dispersible and crushed formulation groups, respectively.

When estimated by the Kaplan- Meier method, at Day 42 the incidence of new P. falciparum infections was 19.8% vs 23.6% in the PQP/DHA dispersible and crushed formulation groups, respectively (ITT population); similar results were obtained in the PP population.

In addition, when estimated by the Kaplan- Meier method, at Day 42, the incidence of recrudescences was 3.1 % vs 1.3% in the PQP/DHA dispersible and crushed formulation groups, respectively (ITT population); similar results were obtained in the PP population.

As for PCR-Corrected /Uncorrected ACPR, the comparison between the PQP/DHA dispersible and crushed formulation groups on time to new infections and time to recrudescences were not statistically significant in both ITT and PP populations by Log-Rank tests.

The observed cases of recrudescence by Day 28 were comparable with those observed in the previous Phase III study in African children in which the rate of true recrudescence was 1.4% in the ITT population and 1.5% in the PP population. In the same Phase III study, by Day 42, the recrudescences were equal to 4.0% and 4.3% in the ITT and PP populations, higher than in the present study in which ≤ 2.5% of patients had recrudescences.

Treatment Failure: Other than new infections/recrudescences other reasons for treatment failure were:

There was only one ETF in the study and this was related to a complication in severe malaria for a patient enrolled about 48 hours from the starting of the malaria symptoms. The complication occurred about 20 hours after the first study drug intake and could be related to the late starting of the anti-malarial treatment.

There only patient who experienced an ETF was randomized to the dispersible formulation group. This patient (site 03 screening number 22 randomisation number 1085) presented at site three days after the start of symptoms (cough and cold) and fever. In those previous three days, the child was treated at home with paracetamol and vitamins. During the first day of treatment, the patient presented high fever and about 20 hours after the first study drug intake developed polypnea and severe anaemia. Worsening in severe malaria was diagnosed and the child was treated with parenteral artesunate. He finally recovered.

Repeated vomiting was more frequent in the dispersible formulation group respect to the crushed formulation group (10 vs 2 cases) while withdrawal before Day 28 was more frequent in the crushed versus the dispersible formulation group, 9 vs 4 cases, respectively.

Overall, the sum of the ETFs and LTFs in the ITT population was equal to 15 cases (7.5%) in the PQP/DHA dispersible formulation group and 4 cases (4.0%) in the crushed formulation group. In the PP population the cases were 15 (8.7%) and 4 (4.8%) respectively for the dispersible and crushed formulation groups. This difference was due mainly due to the difference in LTFs related to new infections.

By Day 42, there was an increase in number of LTFs in the crushed formulation group; therefore, the final figures of treatment failures were 42 episodes (21.2%) in the PQP/DHA dispersible formulation group and 22 (22.1%) in the PQP/DHA crushed formulation group.

Proportion of aparasitaemic patients and time to parasitaemia clearance: In ITT population, less than half of the patients were still parasitaemic (46.2% and 48.5% in the dispersible and crushed formulation groups) at Day 1 afternoon check and only 3.0% and 2.0% were still parasitaemic at Day 2 afternoon check. On Day 3 for dispersible formulation group, all patients but one were aparasitaemic, belonging to the dispersible group. This patient was then found aparasitaemic at the check on Day 7. There were no differences in the parasitaemia clearance time in both the two studied groups, as indicated by the Log-Rank test (p-value=0.653).

Proportion of afebrile patients and time to fever clearance: In the ITT population, on Day 0, 40.2% vs. 38.4% of patients were afebrile in the dispersible and crushed formulation groups, respectively. At the end of Day 1, 82.4% vs. 89.9% of patients were afebrile; on Day 3 almost all patients were afebrile. The analysis of the fever was not considered a relevant point in the evaluation of the efficacy of treatment since many patients had previous or concomitant administration of antipyretic drugs.

Proportion of patients with gametocytes: At enrolment, in the ITT population, only 5% of patients in both groups presented gametocytes, which quickly disappeared in the next few days. Almost all the patients did not develop gametocytes during the course of the study. However, no conclusion can be drawn about the efficacy of the drug on gametocytes because of the limited number of patients presenting gametocytes in the infant population.

Fever clearance time and gametocyte density over time: due to the quick disappearance of both fever and gametocytes the survival analyses relevant to those two parameters were not carried out.

Summary of Safety

Extent of Exposure: The compliance with the study drug for the whole treatment period was good in all the patients, except those who stopped treatment due to repeated vomiting.

Adverse Events: The proportion of patients experiencing at least one TEAE was slightly higher in patients treated with the crushed formulation (84.9%) with respect to patients treated with the dispersible formulation (80.4%). In particular, vomiting (25.1% vs. 32.3%) was more frequently reported in the crushed formulation group with respect to the dispersible formulation group.

In the dispersible formulation group, 160 out of 199 patients (80.4%) had at least one AE during the study. About a third of patients experienced at least one AE, which was considered related to the treatment (n = 67, 33.7%), while n = 93 (46.7%) experienced at least one AE, which was considered unrelated. For 115 patients (57.8%) the AEs were classified as mild, for 44 patients (22.1%) the AEs were classified as moderate, and only for one patient (0.5%) it was classified as severe AE.

Vomiting was the most frequently reported AE (n = 50 patients; 25.1%) and was often associated with drug intake (n = 45; 22.6%). Anaemia was frequently reported during the study (n = 22; 11.1%), assessed as not serious, unsuspected and expected, and was usually temporally associated with P. falciparum infection. Only one case (0. 5%) was considered suspected. Other common AEs such as diarrhoea (n = 14; 7.0%), bronchitis (n = 20; 10.1%), gastroenteritis (n = 9; 4.5%), decreased appetite (n = 7; 3.5%), general respiratory tract infection (n = 20; 10.1%), rhinitis (n = 13; 6.5%), cough (n = 12; 6.0%), flu (n = 7; 3.5%) and pyrexia (n = 12; 6.0%) were mostly considered to be unrelated to the study treatment.

In the crushed formulation group, 84 out of 99 patients (84.9%) had at least one AE during the study. Among these patients, 42 (42.4%) experienced AE considered as suspected related to study treatment and 42 (42.4%) experienced AE unsuspected related to the study treatment by Investigators. For 58 out of 99 patients (58.6%), the AEs were classified as mild, for 25 patients (25.3%) the AEs were classified as moderate and only for one patient (1.0%) it was classified as severe AE. Vomiting was the most frequently reported AE (n = 32 patients; 32.3%) and was often associated with drug treatment (n = 31; 31.3%). Anaemia was also frequently reported as AE (n = 12; 12.1%) and was often associated with P. falciparum infection. All these cases were assessed as not serious, unsuspected and expected. Other common AEs such as diarrhoea (n = 8; 8.1%), bronchitis (n = 11; 11.1%), general respiratory tract infection (n = 9; 9.1%), rhinitis (n = 3; 3.0%), pyrexia (n = 7; 7.1%) were mostly considered to be unrelated to the treatment by Investigators.

The AEs profile for both dispersible and crushed formulation groups was very similar in terms of type and frequency of events and was consistent with that expected in young children with acute malaria in Africa.

Serious adverse events, deaths and other significant adverse events: For 2 patients out of 298, the observed AEs were reported as STEAEs, one per treatment group (0.5%. vs. 1.0% in the dispersible and crushed formulation groups, respectively), both assessed as unrelated to the study treatment by Investigators. The STEAE in the crushed formulation group resulted in death.

Table 12.5.3-1: Significant Adverse Events Causing Early Discontinuation in Dispersible Formulation group (Safety Population)

Patient No.	Age (months)	Sex	Preferred Term	Onset	End	Severity	Relation to PQP/DHA
02-001-1001	07	Male	Vomiting	Day 0	Day 0	Mild	Suspected
02-005-2002	09	Female	Vomiting	Day 1	Day 1	Moderate	Suspected
02-020-1004	10	Male	Vomiting	Day 0	Day 0	Moderate	Suspected
03-022-1085	12	Male	Malaria (Severe)	Day 1	-	Severe	Unsuspected
04-098-1079	10	Male	Vomiting	Day 0	Day 0	Mild	Suspected
04-105-2105	12	Female	Vomiting	Day 2	Day 2	Moderate	Suspected
04-117-2116	09	Female	Vomiting	Day 0	Day 0	Moderate	Suspected
04-122-1094	07	Male	Vomiting	Day 0	Day 0	Mild	Suspected
05-001-2048	08	Female	Vomiting	Day 0	Day 0	Mild	Suspected
05-046-2102	07	Female	Vomiting	Day 1	Day 1	Mild	Suspected
05-048-1082	07	Male	Vomiting	Day 1	Day 1	Mild	Suspected

Source: Table 14.4-14.

Table 12.5.3-2: Significant Adverse Events Causing Early Discontinuation in Crushed Formulation group (Safety Population)

Patient No.	Age (months)	Sex	Preferred Term	Onset	End	Severity	Relation to PQP/DHA
04-071-1066	09	Male	Vomiting	Day 0	Day 0	Mild	Suspected
05-054-2111	10	Female	Vomiting	Day 0	Day 0	Mild	Suspected

Source: Table 14.4-14

Clinical laboratory evaluation: At recruitment, most of the patients were anaemic. During the course of the study, the anaemia ameliorated. At baseline AST, ALT and total bilirubin levels were clinically significantly increased in patients of both dispersible (11.6%, 3.0% and 2.0%, respectively) and crushed (16.2%, 3.0% and 3.0%, respectively) formulation groups, this was expected for malaria patients. Most of these abnormalities quickly resolved.

Vital signs, symptoms and clinical examination: At enrolment, most of the patients had fever and high pulse rate. No significant differences of pulse rate and body temperature were found between treatment groups. Fever was resolved in most of the patient by Day 1.

The most frequently observed symptoms reported as AEs during the study were vomiting, diarrhoea, anaemia, respiratory infections, cough and fever.

The most common abnormal clinical examination findings at Day 0 between treatment groups regarded ear-nose-throat (9.1% vs 5.1%), lungs (32.7% vs 23.2%) and abdomen (13.6% vs 14.1%). After Day 0, no relevant differences between treatment groups for any other abnormal examination finding were observed.

QTc prolongation, potential and descriptive ECG and QTc analyses (centralised data): No arrhythmias were reported during the study. QTcF interval prolongations were reported as AESIs in 23 patients (11.6%) of the dispersible formulation group and 15 patients (15.2%) of the crushed formulation group. All cases were assessed as: Non Serious, Mild in intensity, Suspected and Expected per SmPC. All reported cases occurred in patients in which the food intake restriction could not be respected due to the small age of the patients.

QTc interval prolongation was assessed using both Fredricia's and Bazett's correction methods but it must be considered that both correction formulas are biased by the physiological high HR presented by the young children, and exacerbated by the ill status and fever. At baseline, the values of QT/QTc were not significantly different between treatment groups using both correction methods. Of note, applying the two correction methods, the mean of the baseline evaluations differs drastically. In fact, the dispersible formulation group showed a mean baseline QTcF interval equal to 354 msec while the mean baseline QTcB became 415 msec. Similarly, in the crushed formulation group the mean baseline values were 359 and 421 for QTcF and QTcB, respectively. In both cases, there was a difference of about 60 msec between the values of QTc intervals when a different correction method was applied.

This difference deposed for a bias introduced by the high heart rate commonly recorded in young children suffering from an acute episode of malaria, and by its association with fever, which results in an increase of sympathetic activity. All these conditions are well known factors that affect QT/QTc interval duration. Furthermore, Fridericia's correction formula tends to over-correct QT duration when heart rate values exceed 130-135 beats per minute, and the result of this correction can have determined lower baseline QTcF values than real.

Fridericia's Method: The change in QTcF interval from baseline (Day 0 pre-dose) was detectable on Day 2 pre-dose, with a tendency to QTcF prolongation being observed in both groups with a parallel reduction in HR.

At Day 2 post-dose, this change became more relevant, with respect to Day 0, with 22 patients in the dispersible group (11.1%) and 14 patients in the crushed group (14.1%) manifesting a QTcF over 60 msec. These QT interval prolongations were transient and quickly resolved. In fact, at LAD, the QTcF prolongation tended to normalization, with only one patient (0.5%) in the dispersible formulation group and two patients (2.0%) in the crushed formulation group still presenting an increment of QTcF higher than 60 msec.

Bazett's Method: The change in QTcB interval from baseline (Day 0 pre-dose) was detectable on Day 2 pre-dose, with a tendency to QTcB prolongation being observed in both groups with a parallel reduction in HR. In fact, 2.0% of patients showed a QTcB prolongation > 60 msec in both the treatment groups.

At Day 2 post-dose, this change became more relevant, with respect to Day 0, with 13 patients in the dispersible group (6.5%) and 3 patients in the crushed group (3.0%) manifesting a QTcB over 60 msec. Only one patient in the dispersible group showed a QTcB interval prolongation over 500 msec (508 msec) on Day 2 post-dose starting from a baseline level at Day 0 of 456 msec. These QT interval prolongations were transient and quickly resolved.

At LAD, the QTcB prolongation tended to normalization, with none of patients presenting an increment of QTcB higher than 60 msec, in both the treatment groups.

There were no relevant differences between treatment groups at baseline (Day 0), at Day 2 pre-and post-treatment and at Day 7 in HR, PR and QRS.

A relevant and comparable reduction in HR in both groups was observed at Day 2 (pre- and post-treatment) accompanied with a related prolongation of the PR interval. These findings were partially due to the resolution of the malaria.

As discussed before, this lengthening of QTc from baseline to Day 2 was probably influenced by the high HR associated with presence of fever and activation of the sympathetic activity. All these considerations strongly suggest that the QT/QTcF increase exerted by Eurartesim could be overestimated.

In summary:

-Virtually in no case, regardless the observed absolute increase of the value of the QTcF interval possibly related with the study treatment and the drug administration conditions, the QTcF interval duration exceeded the limits considered normal/borderline for QTcF duration in such patient population (450-470 msec).

-No cases of QTcF> 500ms were reported.

-No case evolved in any form of rhythm disturbance.

-The QTcF interval prolongation >60 ms was mainly observed 3-6 h after the third and last drug administration.

Overall, the changes in QT interval (either QTcF or QTcB) observed during the study treatment period were never associated with clinical signs of cardiotoxicity.

Conclusions

The primary objective of this study was to assess the PK of Eurartesim (PQP/DHA) in a new water dispersible formulation, film coated tablet, and crushed film coated tablet in venous blood samples during and after a therapeutic course of Eurartesim in a paediatric population. The primary endpoint was to estimate the population and individual PK parameters and variability of PQ and DHA in paediatric populations administered with Eurartesim.

Among the secondary objectives of the study was to assess the PK/PD relationship of Eurartesim in malaria patients (adult and paediatric populations). The objective was to obtain a comprehensive PK/PD relationship for DHA and PQ after administration of Eurartesim as a film coated tablet, crushed

film coated tablet, or water dispersible tablet in malaria patients. Modelling of P. falciparum parasite density was performed and the effect of covariates on the PD modelling was explored.

The other secondary objectives were to evaluate the efficacy of the Eurartesim formulations (dispersible and crushed tablets) in treating uncomplicated malaria episodes and their ability in protecting patients from reinfections, to assess the PK/PD relationship of Eurartesim in malaria patients (adult and paediatric populations) and to evaluate safety and tolerability of Eurartesim in infants.

The clinical results showed that both formulations confirmed the satisfactory safety and efficacy of Eurartesim. The clinical efficacy data confirmed that Eurartesim crushed film coated tablet and the water dispersible formulations were efficacious in treating the 300 real male and female paediatric patient aging between 6 and 12 months involved in the present study. The safety profile of Eurartesim was confirmed and the two different formulations compared in the study were substantially similar.

CHMP comments:

The applicant has presented PK and PK/PD modelling data with 200 simulated patients, using the results of the sparse PK sampling performed in the current paediatric study. However the two different strengths of the dispersible formulation have been grouped together, so it is not possible to ascertain the effects of the two tablets separately.

No PK parameters on the real paediatric population have been presented. Similarly the number of subjects in each age and weight band of the real population have not been presented. The simulated weight only goes up to a maximum of 11.95 kg whereas the higher strength tablet is also for patients >13kg.

According to the simulation, the BE criteria was met for the PQ component but not for DHA, which for both Cmax and AUC was lower for the new formulation. However the PD effects did not appear to be different. It is possible that lower values could be due to inclusion of patients that vomited, although according to the model such patients were excluded.

Over 95% patients were considered treatment compliant however it is not clear how many adhered to the food restriction. The first dose was given irrespective of food intake, on the other hand vomiting was progressively less from D1 to D3. Therefore clarification is required of the effect of food on PK, safety and efficacy.

The patients in the dispersible and crushed groups appear generally balanced in their baseline characteristics, however lung infections were higher in the former. The applicant should comment. The number of withdrawals due to vomiting were also much higher in the dispersible group.

The overall efficacy of the dispersible tablet appears similar to that of the crushed film-coated tablet. However there were a large number of late treatment failures. These however seem to be similar to the crushed group by D42.

No new adverse events of concern were identified and the safety data from the paediatric patients in this study were consistent with the known safety profile of eurartesim. However the high incidence of vomiting, particularly on day 1 and soon after taking the medication is a cause for concern. This resulted in treatment withdrawals and treatment failures.

The considerable number of QT-prolongations observed is also of concern, particularly > 60 ms in 6.5% of the subjects treated with the dispersible tablets and one case of QTcB over 500 ms.

The increase in QT prolongation seen could be due to inaccurate determination as the formulae used are known to be affected by raised heart rate. The fact that “all reported cases occurred in patients in

whom the food intake restriction could not be respected due to the small age of the patients" is alarming and seriously questions the suitability of DHA/PQP for malaria therapy in this age group. The MAH is asked to critically discuss this issue, also in context with alternative treatment options for this age group. Further, ways to mitigate this risk should be explored such as possible shorter feeding time if considered essential during the 3 hours before/after eurartesim intake, iv supplementation etc; although it is acknowledged that these will be difficult to implement. Neverthless this will need clinical monitoring, which may not be feasible in low income and low resource settings.

There was one death in the crushed group, considered unrelated, and another SAE in the dispersible group of severe malaria and intestinal mycosis, considered unsuspected and unexpected.

The population PK and PKPD modelling is acceptable and adequate for simulations. It should be noted that patients who vomited were excluded from the analysis. Despite lower exposure for DHA yet comparable exposure for PQ, simulated time to parasite clearances was comparable between the old crushed and the new dispersible tablet.

1.3.3. Discussion on clinical aspects

The applicant has submitted a clinical overview and the complete CSR for this paediatric study.

The present study was a randomized open label study of 300 children (aged 6 to 12 months); a comparison between the approved tablet, crushed and administered with water, and the dispersible tablet was conducted in order to evaluate population pharmacokinetics, efficacy and safety parameters. The two arms were allocated with a ratio of 2:1 (dispersible vs crushed film coated formulations).

The clinical study demonstrated similar efficacy results. At day 28, the PCR-corrected ACPR was 86.9% (pure-ITT) and 98.3% (PP) in the dispersible tablet group, and 84.9% (pure-ITT) and 100% (PP) in the crushed tablet group. At day 42, it was 85.9% (pure-ITT) and 96.5% (PP) in the dispersible tablet group, and 82.8% (pure-ITT) and 96.4% (PP) in the crushed tablet group.

The safety profile for the dispersible and crushed tablet groups was similar in terms of type and frequency of Adverse Events and was consistent with that expected in young African infants with uncomplicated acute malaria. There were no new or unexpected safety findings from the paediatric patients enrolled in the study, although the incidence of vomiting was high in both groups. There were a large number of SAEs in both groups, reflecting the serious condition of these patients.

According to the MAH, the results of this study confirm the possibility to introduce an appropriate formulation for paediatric patients in order to reduce the dose and extent of exposure variability, so as to address a high medical need, mostly in endemic areas, with a significant improvement of the compliance.

The MAH also confirms that this paediatric study does not influence the benefit risk profile for Eurartesim: therefore no further regulatory action is envisaged at this stage.

2. CHMP's overall conclusion and recommendation

Overall conclusion

On the basis of the results of this paediatric study, there is currently no change in the benefit-risk profile of Eurartesim for the existing indications. Therefore, no SmPC changes are needed based on the results of this study at present.

The introduction of a new formulation for the paediatric population is considered desirable to enable easier intake and to improve compliance. The dispersible formulation showed almost similar safety and efficacy compared to the crushed formulation despite the inequivalent exposures seen on BE modelling. The risk of QT prolongation would need to be mitigated by providing proper risk minimisation strategies, including full clinical and ECG monitoring, to the maximum extent possible.

Further improvements in palatability and/or the development of an oral solution are also considered desirable.

☒ **Fulfilled:**

No regulatory action required.

3. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Information on module 3 should be provided as to determine the qualitative and quantitative composition, manufacturing process(es) and pharmaceutical performance characteristics (in-vitro dissolution results) of the new formulations.
2. The batch size for each of the formulations should be stated.
3. Please clarify the number of patients that were included/treated per weight band (dosing group) and age band, particularly patients who were treated with the lower strength formulation.
4. The patients in the dispersible and crushed groups appear generally balanced in their baseline characteristics, however lung infections were higher in the former. The applicant should comment.
5. BE results have been presented with simulations only. Please clarify whether this was attempted in the real population despite the small number of samples.
6. Information on PK/PD, efficacy and safety must be provided for the two dispersible formulation groups separately.
7. Please clarify how many participants were fully/partly/non- adherent to the food restrictions per dosing group.
8. In the efficacy section it is mentioned that the incidence of vomiting was higher in the dispersible group while in the safety section it is stated it was higher in the crushed tablet group. Please clarify.
9. Vomiting is still a problem with the new formulation. The MAH should critically elaborate on the adequacy of the taste masking of the dispersible tablets. Further suggest how this concern of vomitting could be mitigated. Is further development planned to improve palatability?
10. As the study participants were too young to report on any acceptability/palatability issues with the three formulations, the MAH should comment if taste panels (adult subjects) have been used during the formulation development or how acceptability of the formulation was evaluated.
11. QT prolongation is also a concern. As this is more particualrly seen in patients whom the food intake restriction could not be respected due to the small age of the patients, the MAH is asked

to critically discuss the suitability of DHA/PQP for malaria therapy in this age group, also in context with alternative treatment options for this age group. Ways to monitor such patients and ways to mitigate this risk should be explored.

12. The percentage of LTF is twice as high in the dispersible tablet group as compared to the group receiving crushed tablets. The applicant should critically discuss these imbalances and the potential consequences in clinical practice.
13. Information on the severity of vomiting in the different treatment groups should be presented.
14. There is lack of BE, safety concerns and thereby possible consequent efficacy concerns (eg lack of efficacy if the entire dose can not be taken due to vomitting) despite similar PK and PK/PD effects seen on modelling with the dispersible formulation compared to the crushed formulation. Therefore it is difficult to justify the use of this formulation, as is, in the proposed paediatric population. The applicant should fully justify their position.
15. Further, requirement of adherence to food restrictions, need for clinical and ECG monitoring etc is difficult in low resource settings. The applicant should justify how this will be achieved.

MAH responses to Request for supplementary information

1. Information on module 3 should be provided as to determine the qualitative and quantitative composition, manufacturing process(es) and pharmaceutical performance characteristics (in-vitro dissolution results) of the new formulations:

Rapporteur's comment:

Information on module 3 has been provided as requested including details of the qualitative and quantitative composition of the formulation, manufacturing process(es) and pharmaceutical performance characteristics (in-vitro dissolution results) of the new formulations.

The information provided is considered acceptable. Point resolved.

2. The batch size for each of the formulations should be stated:

Rapporteur's comment:

The batch data have been provided as requested.

Response considered acceptable. Point resolved.

3. Please clarify the number of patients that were included/ treated per weight band (dosing group) and age band, particularly patients who were treated with the lower strength formulation:

Summary of MAH's response:

The percentage of infants weighing < 7 kg BW was slightly higher in the water dispersible formulation group than in the crushed tablet formulation group, being about 21.1 versus 11.1%, respectively; conversely, patients aged < 9 months were quite balanced for age between groups, being 39.7 versus 36.4% in the water dispersible formulation group and in the crushed tablet formulation group respectively.

Considering the limited numbers obtained when patients were stratified by age and dose, we may assume that the balance among groups was acceptable.

Rapporteur's comment:

The MAH's responses are considered acceptable. Point resolved.

4. The patients in the dispersible and crushed groups appear generally balanced in their baseline characteristics, however lung infections were higher in the former. The applicant should comment:

Summary of MAH's response:

In conclusion, in most of the cases cough is the only symptom at lung level and therefore most likely related to the malaria episode. Being this event resolved after a few days, together with the relief from acute malaria, it can reasonably be correlated with the malaria episode. The noted mild imbalance between the treatment groups was only detected at baseline, before any drug administration, therefore it was judged as caused by randomness and unrelated with the treatment, and not causing any bias in the study results.

Rapporteur's comment:

There does not appear to be an increased incidence of lung infections other than cough. Response considered acceptable. Point resolved.

5. BE results have been presented with simulations only. Please clarify whether this was attempted in the real population despite the small number of samples.

Summary of MAH's response:

In the real population, the increase in PQ bioavailability due to food effect was not observed. Annerberg et al 2011 and Tarning et al 2014 reported similar findings: small amount of food, mainly milk, did not alter the absorption of PQP in malaria patients.

After a single dose of PQ, the analysis on dose corrected systemic exposure parameters confirmed the BE between the water dispersible formulation and crushed tablet formulation in terms of AUC, while Cmax was slightly lower for the new formulation compared to the old one. As expected, no food effect was observed for DHA absorption the BE analysis on dose-normalized systemic exposure parameters confirmed the results obtained through simulation approach, although in the real population the relative bioavailability of DHA was more than 10% higher than in the simulated population.

Rapporteur's comment:

The simulated and real life results are not completely concordant. There does appear to be some effect of food, however this does reflect the normal situation where children are likely to be given some milk/ other food despite the restrictions being mentioned. It is further noted (see below), that despite slight differences in the AUC and Cmax for both PQ and DHA in the simulated vs real life results and between crushed and dispersible formulations, the clinical outcome parameters are more or less similar.

Therefore the Rapporteur is prepared to accept the response. Point resolved.

6. Information on PK/PD, efficacy and safety must be provided for the two dispersible formulation groups separately.

Summary of MAH's response:

PQ and DHA pharmacokinetics, efficacy and safety parameters were similar among dose and formulation groups.

Rapporteur's comment:

Late failures at d42 are about 30-35%, with greater incidence in the low dose, low weight category ie the youngest children for both formulations. There was a slight imbalance in groups with the percentage of infants weighing < 7 kg BW being slightly higher in the water dispersible formulation group than in the crushed tablet formulation group (21.1 versus 11.1%). This did not appear to be due to variable exposure of the actives, since DHA exposure was lower in all age groups for the dispersible compared to the crushed formulation.

The Rapporteur is prepared to accept the response. Point resolved.

7. Please clarify how many participants were fully/partly/non-adherent to the food restrictions per dosing group.

Summary of MAH's response:

From the study recordings, the adherence to the food restrictions required for Eurartesim seemed quite difficult in patients below 13 kg body weight and 12 months of age.

Overall, slightly less than 36% were fully or partially compliant of with food restrictions, the compliancy resulting quite balanced between the dosing groups.

Rapporteur's comment:

There were only about 36% subjects who were fully or partially compliant with food restrictions, this was quite balanced between the treatment groups. The main food given was milk in the majority of subjects, followed by maize.

In these young patients this non-compliant behaviour is not unexpected.

Response considered acceptable. Point resolved.

8. In the efficacy section it is mentioned that the incidence of vomiting was higher in the dispersible group while in the safety section it is stated it was higher in the crushed tablet group. Please clarify.

Summary of MAH's response:

In conclusion, there was a small difference in *repeated vomiting* between the two treatment groups, possibly related to the clinical conditions of the patients. When *single vomiting episodes* are considered, the difference observed between treatment groups is more evident and in favour of the dispersible formulation administration. For more details about the vomiting distribution within the weight categories, please refer to the answer provided for Question 13.

Rapporteur's comment:

Response considered acceptable. Point resolved.

9. Vomiting is still a problem with the new formulation. The MAH should critically elaborate on the adequacy of the taste masking of the dispersible tablets. Further suggest how this concern of vomiting could be mitigated. Is further development planned to improve palatability?

Summary of MAH's response:

In conclusion, the rate of vomiting observed in the present study is most likely to be related to the malaria symptoms and the low age of children rather than to the drug formulation. The data evidenced that the utilisation of a taste masked dispersible formulation has reduced the vomiting frequency in this population.

The MAH believes that all the efforts in order to improve the drug palatability have been done in the present formulation and that no other development strategies can be applied in order to further reduce the vomiting in this young population.

Rapporteur's comment:

No specific palatibility studies have been carried out. The choice of flavour is based on studies with other anti-malarials. This may be reasonable, although despite the dissolution test results it is a possibility that taste may be affected.

Neverthless, this may also be related to the age of the patients with youngest patients finding it harder to take the tablets than older children.

Response considered acceptable. Point resolved.

10. As the study participants were too young to report on any acceptability/palatability issues with the three formulations, the MAH should comment if taste panels (adult subjects) have been used during the formulation development or how acceptability of the formulation was evaluated.

Summary of MAH's response:

A microencapsulation technology was utilized for masking the bitter taste of PQP; furthermore the powder was formulated adding sweeteners and flavour to obtain a good palatability, evaluated through no-formal lab test. References[1]

Rapporteur's comment:

No specific palatibility studies have been carried out. The choice of flavour is based on studies with other anti-malarials. This may be reasonable, although despite the dissolution test results it is a possibility that taste may be affected. It is mentioned that the microencapsulated powder lacked any bitter taste when rapidly swallowed- this may not be possible to do in young children.

Neverthless, this may also be related to the age of the patients with youngest patients finding it harder to take the tablets than older children.

Adult tasting panel tests would have been helpful, even though it is known that sensitivity of taste differences are known between children and adults.

The Rapporteur is prepared to accept the response. Point resolved.

11. QT prolongation is also a concern. As this is more particularly seen in patients whom the food intake restriction could not be respected due to the small age of the patients, the MAH is asked to critically discuss the suitability of DHA/PQP for malaria therapy in this age group, also in context with alternative treatment options for this age group. Ways to monitor such patients and ways to mitigate this risk should be explored.

Summary of MAH's response:

Acute malaria illness has significant effects on the QT interval. When admitted to clinics, patients are usually febrile, anxious, upright, tachycardic and often anorexic. The sympathetic nervous system is activated and the QT interval is shortened. As the patient recovers, often lying in bed, the fever settles, appetite returns, the heart rate declines and the QT interval lengthens. The difference between the

[1] S. Abdulla, B. Amuri, A. M. Kabanywanyi, D. Ubben, C. Reynolds, S. Pascoe, S. Fitoussi, C.Yeh, M. Nuortti, R. Séchaud, G. Kaiser, G. Lefèvre. Early clinical development of artemetherlumefantrine dispersible tablet: palatability of three flavours and bioavailability in healthy subjects. Malaria J. 2010, 9:253-261.

shortened QT interval before treatment and the day-3 normalized QT interval (which often coincides with the peak of antimalarial drug concentration) may be misattributed to a drug effect. In addition, usual QT correction formulae designed to normalize the QT interval tend to "overcorrect" (i.e., the QTc interval appears shorter) at fast heart rates and "undercorrect" (i.e., the QTc interval appears longer) at normal or slow heart rates. These factors should be taken into account when interpreting results from ECG safety studies in malaria patients (White 2007). According to this consideration, the actual study results were re-analysed applying a study specific correction factor (QTcSS) and submitting all methods to a linear model including the changes in RR as primary explanatory variable.

The QTcSS showed to be the best correction method in order to estimate differences between the baseline QT interval value and the 4h post-treatment value. When this correction method was applied to the data of the present study, QT interval prolongation drastically dropped down with respect to the values obtained when Fridericia's or Bazett's formula were applied.

Interestingly, the covariate "food condition" did not show any influence in the model, demonstrating that the small amount of food taken by these children has not a significant relevance in term of the cardiotoxicity risk related to an increase of QT interval. These observation is also corroborated by the results obtained for the piperaquine concentration data reported in the answer to question 5 where the results show that there is no significant difference in the plasma piperaquine concentration when the DHA/PQP formulations have been administered with or without food.

The lack of significant effect of a small amount of food on piperaquine pharmacokinetics was also previously demonstrated in a pharmacokinetic study conducted in malaria patients treated with DHA/PQ in fasting condition or co-administered with 200 mL of milk containing about 6.4 g of fat (Annerberg et al. 2011).

Considering the QT interval prolongation observed when the QTcSS method was applied and the observation that piperaquine pharmacokinetics is not significantly different between infants treated under fasting or fed condition (see answer to question 5), the MAH believes that the risk associated with a small food co-administration in malaria children is negligible, on the other side, the benefit offered by having a more appropriate paediatric formulation of DHA/PQP in the paediatric treatment portfolio is of great relevance to keep ACT treatments efficacious as long as possible in view of the spread of artemisinin resistance already reported in the greater Mekong region (Yeung et al. 2009; Fairhurst et al. 2012).

Rapporteur's comment:

The applicant contends that due to the various reasons for increased heart rate in children, both physiological and pathological, it is difficult to accurately measure QT prologation using the standard methods. Therefore a modification has been applied, based on the finding that only gender and not food seemed to affect the QT interval. This method is not considered to be fully validated and therefore caution is required when interpreting the results.

It is agreed that an efficacious anti-malarial regimen is required in the face of increasing resistance to other therapies and that Eurartesim may, to some extent, be able to step in. It is also highly unlikely that all children will adhere to the strict no food restriction. Therefore taking a pragmatic view, it is considered that the risk of QT prolongation is outweighed by the benefit of a successful treatment.

The Rapporteur is hence prepared to accept the response. Point resolved.

12. The percentage of LTF is twice as high in the dispersible tablet group as compared to the group receiving crushed tablets. The applicant should critically discuss these imbalances and the potential consequences in clinical practice.

Summary of MAH's response:

The unbalanced distribution of patients within the two treatment groups at the site 03 and the disappearance of any difference in LTF between treatment groups at Day 42 support the conclusion that the noted Day 28 imbalance within the two treatment groups is not based on real differences between the two drug formulations compared in this study.

Rapporteur's comment:

The applicant contends that the difference in LTF observed at d28 but not a d42, could be due to imbalances in patient randomisation at two sited. This may be a possibility however a true effect is also likely as the difference was much less at d42. No other pausible explanation has been provided.

The Rapporteur is prepared to accept the response. Point resolved.

13. Information on the severity of vomiting in the different treatment groups should be presented.

Summary of MAH's response:

In conclusion, in most of the cases vomiting was of mild intensity and more frequent in infants treated with the crushed formulation. Since smaller children are more likely to vomit antimalarial treatments (WHO Guidelines for the treatment of malaria, 3rd Edition Section 5.2) when they are hill and febrile respect to the older ones, the evidence of reduced number of vomit episodes when the dispersible formulation was administered could be considered a sign of better acceptance of the dispersible formulation respect to the crushed one.

Rapporteur's comment:

No severe case of vomitting was reported in either group, with mild and moderate vomitting being lower and higher respectively in the dispersible and crushed formulations.

Apart from taste, the infection itself and age of the patient may make them prone to vomitting.

The Rapporteur is prepared to accept the response. Point resolved.

14. There is lack of BE, safety concerns and thereby possible consequent efficacy concerns (eg lack of efficacy if the entire dose cannot be taken due to vomiting) despite similar PK and PK/PD effects seen on modelling with the dispersible formulation compared to the crushed formulation. Therefore, it is difficult to justify the use of this formulation, as is, in the proposed paediatric population. The applicant should fully justify their position.

Summary of MAH's response:

Overall, in MAH opinion, there are no major concerns about the efficacy and the safety of the new formulation compared to the crushed tablet formulation.

In addition, the following considerations have to be taken into account for judging the clinical value of having a new pediatric Eurartesim formulation as an antimalarial drug:

- the obvious better compliance of this new pediatric formulation compared to the crushed tablet,
- the simplified schedule of Eurartesim as compared to other ACTs

- the importance of having multiple GMP compliant ACTs available on the market, which is definitively needed in the fight against the resistance dread particularly in high transmission territories as Africa.

Rapporteur's comment:

There is a need to balance concerns of bioinequivalence and safety against compliance and the efficacy outcomes. Despite the lower DHA exposures the clinical outcome was more or less similar. QT prolongation was seen but according to the model food has much less effect compared to gender.

The Rapporteur is prepared to accept the response. Point resolved.

However it is considered that proper ECG monitoring, to whatever maximum extent possible in resource poor settings, must be performed to minimise the risk of QT prolongation.

15. Further, requirement of adherence to food restrictions, need for clinical and ECG monitoring etc is difficult in low resource settings. The applicant should justify how this will be achieved.

Summary of MAH's response:

As discussed in answering Question 5, in the real population involved in the ST3073-ST3074-DM12002 study, no increase in PQ bioavailability due to food effect was observed. Annerberg et al 2011 and Tarning et al 2014 reported similar findings: small amount of food, mainly milk, did not alter the absorption of PQP in malaria patients. In light of this observation, the requirement of adherence to food restrictions seems no longer as stringent as in the past, at least for the paediatric population essentially fed with some milk or maize. Consequently, also the stringent ECG monitoring seems no longer necessary.

Rapporteur's comment:

The Rapporteur would not like to dismiss full monitoring of patients so trivially and considers that proper ECG monitoring, to whatever maximum extent possible in resource poor settings, must be performed to minimise the risk of QT prolongation.

Hence the response may be acceptable provided proper risk minimisation strategies, including full monitoring, are put in place. Point considered resolved at this stage.

Annex. Line listing of all the studies included in the development program

Clinical studies

Product Name: Eurartesim Dispersible Tablet

Active substance: Dihydroartemisinin / Piperaquine tetraphosphate

Study title	Study number	Date of completion	Date of submission of final study report
Relative Bioavailability study of a new Eurartesim dispersible formulation versus the crushed marketed Eurartesim film coated formulation orally administered in healthy male volunteers	ST3073-ST3074DM12001	June 4th,2013	May 2nd, 2016*

* Clinical report has been submitted as relevant attachment 3a during the Request for Modification of the Paediatric Plan for Eurartesim (Eurartesim: EMEA-000153-PIP01-07-M04 – RfM).