STATISTICAL ANALYSIS PLAN

A Phase IIIb/IV comparative, randomised, multi-centre, open-label, parallel 3-arm clinical study to assess the safety and efficacy of repeated administration of pyronaridine-artesunate, dihydroartemisinin-piperaquine or artemether-lumefantrine or artesunate-amodiaquine over a two-year period in children and adult patients with acute uncomplicated *Plasmodium* sp. malaria

SP-C-013-11 (WANECAM)

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Abbreviations

ACT	Artemisinin combination therapy
ACPR	Adequate clinical and parasitological response
AE	Adverse event
AL	Artemether-lumefantrine
ALT	Alanine aminotransferase
ASAQ	Artesunate-amodiaquine
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CRF	Case report form
CSR	clinical study report
DHA-PQP	Dihydroartemisinin-piperaquine
ECG	Electrocardiogram
EE	Efficacy evaluable
EMA	European Medicines Agency
GEE	Generalised estimating equation
ICH	International Conference on Harmonization
ITT	Intent to treat
MedDRA	Medical dictionary for regulatory activities
NA	Not applicable
PA	Pyronaridine-artesunate
PCR	Polymerase chain reaction
PCT	Parasite clearance time
PK	Pharmacokinetic
SAP	Statistical analysis plan
TBL	Total bilirubin
ULN	Upper limit of normal range
WHO	World Health Organization

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1. Introduction

This statistical analysis plan (SAP) is based on the study protocol of the WANECAM study SP-C-013-11, dated 19-Nov-2010, with protocol amendments denoted Version 4.0 (14-Jul-2011), Version 5.0 (20-Oct-2011),Version 6.0 (14-Dec-2011), Version 7.0 (29-May-2012), Version 8.0 (26-Oct-2012), Version 9.0 (30-Aug-2013), Version 10 (16-Oct-2013), Version 11 (20-Dec-2013) and Version 12.0 (14-Aug-2014) and the ICH guidelines. All analyses will be performed by DATAMAP GmbH, Freiburg, Germany using SAS®, version 9.3 in a UNIX environment.

This study was designed to compare the incidence rate of malaria episodes in children and adults treated with repeated artemisinin combination therapy (ACT) over a period of 2 years.

The present study randomised patients separately to the following two arms:

(1) Pyronaridine-artesunate (PA) versus comparator (artemether-lumefantrine (AL) or artesunate amodiaquine (ASAQ), depending on the centre's standards)

(2) Dihydroartemisinin-piperaquine (DHA-PQP) versus comparator (AL or ASAQ, depending on the centre's standards)

All summary tables for this study will present all four treatment groups, however, there will be no formal comparison between PA and DHA-PQP.

In the past, there have been several interim analyses of substudies of the WANECAM trial to support the European Medicines Agency (EMA) PA submissions:

- Substudy analyses regarding safety of repeat dosing with PA performed on a subset of patients in 2014 and 2015 (Clinical study report (CSR) dated 24-Feb-14 and CSR Addendum dated 15-Dec-15)
- Substudy analyses of data from patients using the paediatric formulation of PA in comparison to AL in 2014 (CSR dated 26-Sep-14)

These substudy analyses will be re-run on the final locked database and attached to the clinical study report as Appendices. The details of these analyses can be found in the corresponding SAPs, which are embedded in this SAP in Section11.

Exploratory endpoints and analyses as well as data from the separate pharmacokinetic (PK) study are not subject of this SAP.

2. Definitions and data conventions

Episode baseline

Episode baseline for analysis purpose will be defined as the last measurement prior to first study drug administration within each treatment episode, i.e., in general the Day 0 pre-dose assessment. Measurements taken exactly at the time of drug administration will be considered baseline values.

General baseline

General baseline will be the baseline of the first treatment episode. This will be used e.g. to describe the patient's demographic status and medical history.

Episode study days

Study days will be calculated for each treatment episode as actual date minus date of first study drug intake within the current treatment episode, i.e. the day of first study drug intake will be defined as Day 0.

Calculation of age

Age will be calculated from the date of the screening visit and the date of birth and presented as integer value. If the date of birth is not available age as entered on the CRF will be used.

The following SAS code will be used to calculate age where &dob is the date of birth and &dat is the date of visit 1

```
floor((intck('MONTH',&dob,&dat)-(day(&dat)<day(&dob)))/12)
```

Calculation of Body Mass Index (BMI) per episode

BMI will be calculated as weight (kg) / [height (m)]^2 per episode.

BMI will be rounded to one decimal.

Fever

Fever will be defined as axillary body temperature ≥37.5°C, or rectal, oral or tympanic temperature ≥38°C.

Parasitaemia

Presence of parasites will be defined as any *Plasmodium* sp. asexual forms count >0. It will be displayed separately for the *Plasmodium* sp. *falciparum*, *malariae* and *ovale*. All calculations of cure and failure will be based on the *Plasmodium* sp. a patient was diagnosed with at baseline of the actual episode. If a patient presents with more than one *Plasmodium* sp. type at baseline of an episode he/she will be counted for all of them.

Labelling of treatment groups

Treatment groups will be labelled

Pyronaridine-artesunate (if necessary, the abbreviation PA will be used)

Artemether-lumefantrine (if necessary, the abbreviation AL will be used)

Artesunate-amodiaquine (if necessary, the abbreviation ASAQ will be used)

Dihydroartemisinin-piperaquine (if necessary, the abbreviation DHA-PQP will be used)

Definition of visit windows for the analysis of cure rates

With respect to the analysis of adequate clinical and parasitological response rates (ACPR) on specific days, it is necessary that a patient who will be considered 'cured' for a certain day is definitely parasite free (*Plasmodium* sp. asexual forms) on the day of interest. It will be acceptable if a patient comes one day early for a certain visit and *Plasmodium* sp. is negative. If a patient comes later than the envisaged day the cure status will depend on the outcome found on that day. If the patient was parasite-free and no other anti-malaria treatment was given in the meantime, the patient will be considered cured. If the patient has a positive *Plasmodium* sp. count then the patient will be counted as not cured from the day he showed up onwards, and missing for the time point that was missed.

Imputation of missing values

The determination of treatment outcome (ACPR or treatment failure as defined below) at Day 28 will be based on observed parasite count, separately for each *Plasmodium* sp., and temperature measurement and in addition on PCR results for the PCR-corrected rates. These will be calculated and summarised separately for each *Plasmodium* sp. (*falciparum, malariae, ovale*) present at Day 0 of the respective episode. PCR corrected cure rates will only be determined for *P. falciparum*. When the determination of treatment outcome cannot be performed because of missing data, the following imputation method will be applied:

A patient with missing Day 28 parasite count data will be considered as ACPR at Day 28 if he/she is proved to be no treatment failure after Day 28 (i.e. the patient is parasite-free after Day 28). In all other cases the patient will be considered a failure. No other imputations will be performed.

The same methodology will be applied for the classification of treatment outcome at Day 42.

Following these definitions and conventions, the table below provides a summary of treatment outcome in specific situations in accordance with WHO 2009 guidelines. It should be noted that this table is for P. *falciparum* only:

	Treatment outcome Crude ACPR	**Treatment outcome PCR-corrected ***
Withdrawals before Day x: any reason (including lost to follow-up)	exclude from EE, failure in ITT	exclude from EE, failure in ITT
Presence of *P. falciparum* asexual forms before or on Day x but PCR not interpretable or missing	failure in EE and in ITT	exclude from EE, failure in ITT
New infection before Day x	failure in EE and in ITT	exclude from EE, failure in ITT
New infection on Day x	failure	cure
Recrudescence before or on Day x	failure	failure
Missing assessment on Day x, but parasite free (No *P. falciparum* asexual forms) after Day x	cure	cure
Missing assessment on Day x, no more assessment thereafter	exclude from EE, failure in ITT	exclude from EE, failure in ITT
Missing assessment on Day x, new infection (confirmed by PCR) at first assessment after Day x	failure	cure
Missing assessment on Day x, recrudescence (confirmed by PCR) at first assessment after Day x	failure	failure

* PCR analysis only done for *P. falciparum*

For *P. ovale* and *P. malariae*, there is no PCR analysis and the following rules will be applied for crude cure:

	Treatment outcome Crude ACPR
Withdrawals before Day x: any reason (including lost to follow-up)	exclude from EE, failure in ITT
Presence of *Plasmodium* sp. asexual forms before or on Day x	failure in EE and in ITT
Missing assessment on Day x, but parasite free (No *Plasmodium* sp. sexual forms) after Day x	cure
Missing assessment on Day x, no more assessment thereafter	exclude from EE, failure in ITT

Patients who receive rescue medication will be considered a treatment failure from the time of rescue medication intake onwards in the crude analysis. In the PCR corrected analysis the classification of cure / failure will be based on the PCR result in combination with the rescue treatment, i.e., if a patient had a recrudescence which was treated with rescue treatment then the patient will be a failure from that time onwards. If a patient had a new infection (also with a different sp. than at Day 0 of that episode) which was treated with rescue treatment then the patient will be considered "cured" for the time points <= the new infection / rescue treatment will be excluded thereafter from the EE analysis. A patient who received rescue medication due to vomiting of study drug will be a failure in all ITT analyses and excluded from EE analyses. In the ITT analysis patients will be considered as treatment failures.

Patients who receive rescue treatment due to early treatment failure will be considered failures throughout:

- Development of danger signs or signs of severe malaria in the presence of parasitaemia on Days 1, 2, or 3, or a clinical requirement for parenteral treatment. (WHO definition)
- Parasitaemia on Day 2 (>=48-<72 hours) higher than on Day 0 count, irrespective of axillary temperature (WHO definition)
- Parasitaemia on Day 3 with axillary temperature ≥37.5ºC (WHO definition)
- Parasitaemia on Day 3 ≥25% of count on Day 0 (WHO definition)

Malaria episodes temporarily not treated with study drug

Under the following circumstances a patient will temporarily not be treated with study drug:

- Patients with signs and symptoms of severe/complicated malaria requiring parenteral treatment according to the World Health Organization Criteria 2000
- Severe vomiting, defined as more than three times in the 24 hours prior to inclusion in the study or inability to tolerate oral treatment, or severe diarrhoea defined as 3 or more watery stools per day.
- Active acute Hepatitis A, Hepatitis B or Hepatitis C.
- Known significant renal impairment as indicated by serum creatinine of more than 1.5 x ULN.
- Positive microscopy of *Plasmodium* sp. with parasite density greater than 200,000 parasites/µl
- Ongoing SAE NOT related to study drug
- Parasite relapse before Day 28 scheduled visit follow-up
- Use of any other antimalarial agent, other than the one used for malaria rescue treatment or severe malaria.
- Significant arrhythmia or prolonged QTc >450 milliseconds during previous treatment or QTc >450 milliseconds at the time of presentation for re-treatment. Note that the study protocol left it up to the site to chose either Bazett's or Fridericia's correction to calculate QTc.
- Pregnancy or breastfeed at the time of presentation for re-treatment

Such malaria episodes will not be included in any analysis, with the exception of the primary endpoint, the total number of malaria episodes. If a patient was randomised to one drug and subsequently treated with the other such a treatment episode will also be disregarded.

3. Protocol deviations

The study database will be screened for the following major protocol deviations which will lead to an exclusion of a patient's data from the efficacy evaluable analysis.

- Intake of a concomitant medication with known anti-malarial activity which may interfere with the treatment outcome.
- Parasite density of *Plasmodium* sp. >=200,000 /µL.
- Study drug other than randomised taken.

Further, there will be additional non-protocol deviation conditions leading to exclusion from an analysis set which are defined in Section 4 below.

A listing of protocol deviations and other conditions leading to exclusion from an analysis set (See Section 4) will be generated, reviewed and approved by the responsible medical reviewers.

4. Analysis sets

The following patient populations will be defined for the final analysis:

The **overall safety population** will be defined as all patients who received at least one dose of study drug (at any episode).

The **intent-to-treat (ITT) population** will be all patients from the safety population,who had a positive parasite count (any *Plasmodium* sp.) at Day 0, prior to the first dosing within the current episode. The population will be defined per episode, i.e., a patient can be included in one episode but be excluded from another, depending on the *Plasmodium* sp. count.

The **Day 28 efficacy evaluable** population will be defined as all patients from the ITT population:

- who completed a full course of study medication for any treatment episode and had a known primary efficacy endpoint at Day 28 of that episode. A patient will be excluded from the EE analysis if the parasite count is missing at Day 28 and no subsequent parasite count is available after Day 28, and the patient is not previously classified as treatment failure. This includes patients who discontinued from the study before Day 28 for any reason, as well as those who have had a new infection, or a non *P. falciparum* infection before Day 28 and did not have any further parasite assessment. Note that the latter only applies for the analysis of PCR-corrected cure. In the EE analyses of crude cure, patients with a new infection will be included as treatment failure.
- who did not use a concomitant medication with known anti-malarial activity which may interfere with the treatment outcome up to Day 28, except if the treatment was given for the treatment of a new infection. In that case a patient will be considered a failure in the EE analysis of crude cure and will be excluded from the EE analysis of the PCR corrected cure.
- who had any *Plasmodium sp.* for the episode of interest whereby all analyses will be separately by *Plasmodium* sp.
- who did not have major protocol deviations. The list of all protocol deviations will be reviewed with respect to their impact (major/minor) prior to analysis.

The **Day 42 efficacy evaluable population** will be defined in the same way as the primary Day 28 efficacy evaluable population replacing Day 28 with Day 42 in the stated conditions.

The list of patients excluded from the EE population will be reviewed and agreed upon prior to the analysis.

It should be noted that the EE and ITT populations are defined per malaria treatment episode.

Global summary tables that are not based on treatment episodes will include all patients who are part of a certain population at least for one episode.

Analyses of PCR corrected cure will be carried out on the above populations (only for *P. falciparum*), but further excluding patients with a new infection or indeterminate PCR result. These populations will be labelled **Day 28/Day 42 efficacy evaluable population (PCR)**.

4.1 Subgroup analyses

The following subgroup analyses for efficacy and safety are planned for the overall analysis

- Subgroup based on age < 5 yrs, >=5-<18, >=18 years
- Subgroup based on country
- Subgroup based weight <20 kg, >=20 kg
- Subgroup analysis for severely malnourished children, if a sufficient number of patients was recruited. Since the group of such patients is small, their adverse event and liver enzyme data will be listed separately.

Note that there are additional subgroup analyses based on different body weight categories within the substudy analyses.

5. Patient disposition

A summary of the number of patients included in the study by country and centre will be provided.

Patient disposition will be summarised with the number and percentage of patients who were randomised, treated, received at least 1, 2, 3 etc. courses of study drug, who discontinued the study prematurely, and who completed the study by treatment group. Further, the reasons for premature discontinuation from the study will be summarised and a summary of the number and percentage of patients in each analysis population will be provided. The time between each two courses of study drug will also be summarised as continuous variable and categorically (0-30 days, 0-60 days, 0-90 days, 28-60 days, 61-90 days, >90 days). The median time between all treatment episodes per patient will be calculated and summarised in the same way.

6. Demographic data and baseline characteristics

Demographic data and baseline characteristics will be presented by treatment group for the safety and EE populations.

Data will be summarised with number of observations, mean, standard deviation, minimum, median, quartiles, and maximum for continuous variables and with number and percentage of patients for categorical variables. For baseline *Plasmodium sp.* counts the geometric mean will be presented additionally.

Continuous variables: age, height, weight, BMI, *Plasmodium sp.* asexual forms count at baseline of Episode 1, body temperature at screening of Episode 1.

Categorical variables: sex, ethnicity, age category (<18 years further split by <=6 months, >6 months to <1 year, >=1 to <3 years, >=3 to <6 years, >=6 to <18 years, and >= 18 years), body weight category (<20 kg, >=20 kg; <10 kg, >=10 kg)), number (%) of patients with different types of *Plasmodium* sp. present at baseline of Episode 1, fever/no fever at baseline of Episode 1.

Demographic data and baseline characteristics will also be presented for the subgroups.

7. Prior/ concomitant medications

Listings of patients who received rescue medication or who received a non-study drug treatment episode for a temporary non-retreatment with study drugs will be provided.

All concomitant medications, including rescue medication, will be coded according to the most recent version of the WHO dictionary and will be listed by patient.

8. Efficacy analysis

8.1 Primary variable(s)

The following primary efficacy variables are defined in the study protocol:

1. The incidence rate of all (= uncomplicated plus complicated) repeat malaria episodes excluding the first during the two-year observation period. Malaria episodes will be counted irrespective of the parasite sp. The incidence rate will be calculated as the number of malaria episodes divided by the duration in days a patient was observed in the study (last observation date from study completion page minus day 0 of first malaria episode + 1) and multiplied by 730. Please note that this definition is different from the study protocol, which refers only to uncomplicated malaria episode.
2. The uncorrected and the PCR-corrected adequate clinical and parasitological response (ACPR) at Day 28. The ACPR will be summarised separately for *P. falciparum* and other sp. and PCR corrected ACPR will only be provided for *P. falciparum*.
3. The uncorrected and the PCR-corrected adequate clinical and parasitological response (ACPR) at Day 42.

Incidence rates of repeat malaria episodes

The study intends to show non-inferiority of PA or DHA-PQP versus AL or ASAQ in terms of the incidence rate of repeat malaria episodes during the two-year period whereby a non-inferiority margin of 20% was chosen assuming an incidence rate of 3.29 episodes in two years for the comparator. Both PA and DHA-PQP will be compared to both comparators, but not among themselves. For patients recruited in Guinea the overall observation time will be reduced by the time the site was closed during the Ebola epidemic (9-Mar-2015 until 6-Sep-15).

The total number of repeat malaria episodes during the two year period will be analysed by means of a Poisson regression model, carried out separately for PA versus AL / ASAQ and DHA-PQP versus AL / ASAQ.

In case of over dispersion of data (i.e. if the variance is greater than the mean), negative binomial regression analysis will be used.

The analysis will be performed using the SAS procedure GENMOD with the following code:

```
PROC GENMOD data = <datafile name>;
class treatment /param=glm ;
model nepi = treatment /dist=poisson offset=ldur dscale link=log;
run;
```

where nepi is the number of repeat malaria episodes and ldur is the log of the number of days a patient was observed within the study. If negative binomial regression is used dist=poisson will be replaced by dist=negbin.

Further descriptive statistics of the raw incidence rate of malaria episodes will be provided.

Uncorrected and PCR corrected cure rates

Generalised estimating equation (GEE) model will be used to estimate the cure rates over all treatment cycles of all treatments for *P. falciparum*. The GEE model will have the cure as binary dependent variable, randomised treatment group (PA, AL, ASAQ, DHA-PQP) as fixed effects, patient as random effect and will be estimated using the SAS procedure GENMOD with an identity link function and an exchangeable covariance structure The GEE model analysis will be performed for Day 28 and 42 cure rates and PCR corrected cure rates separately.

The following SAS code will be used:

```
PROC GENMOD data = <datafile name>;
class treatment patient;
model event = treatment / dist=binomial link=identity noint;
repeated subject= patient / type=exch;
lsmean treatment /cl alpha=.05;
run;
```

Treatment group estimates with their associated 95% confidence intervals and estimates for the difference between PA and AL/ASAQ and DHA-PQP and AL/ASAQ will be derived from the GEE model. The non-inferiority margin for cure rates is defined in the study protocol as 5%, i.e., a treatment will be considered non-inferior to the other if the lower limit of the 95% confidence interval for treatment group difference from the GEE model is >-5%.

Descriptive statistics of cure rates by treatment episode will be presented separately for each *Plasmodium* sp.

8.2 Secondary efficacy variable(s)

The following secondary efficacy endpoints are defined in the study protocol:

- Re-infection and recrudescence rates over 42 days
- Parasite clearance time and fever clearance time
- Gametocytes density and carriage
- Time until second infection and re-infections

Kaplan-Meier analysis of parasite clearance time (PCT)

PCT will be defined as the time (in hours) from the start of the first dose of study medication within the current episode until the time of the first blood draw which shows disappearance of asexual parasites.

Parasite clearance is defined as zero presence of asexual *P. sp.* which remain at least for a further 48 hours.

PCT will be summarised with Kaplan-Meier estimates by treatment episode. Medians and quartiles will be presented together with their 95% confidence intervals. Patients who did not have (confirmed) parasite clearance will be censored at the time of their last available parasite count within the episode of interest. Also, PCT will be considered censored from the time point a patient received rescue treatment for the episode of interest if the rescue treatment started before parasite clearance or within 48 hour after initial clearance.

Kaplan-Meier curves for PCT will be generated.

Parasite clearance time modelling suggested by Flegg et al. 2011 and 2013 will be part of the exploratory analyses which are not subject of this SAP.

Fever

The fever clearance time will not be analysed since the frequency of fever assessments within this study is not sufficient for a valuable analysis.

Instead the number and percentage of patients with no fever by time point will be summarised. Time points as recorded in the CRFs will be used for summarisation. Day 63 results will not be presented since the observation period until Day 62 was only applied in one centre.

Gametocytes

All gametocyte analyses will be presented for two subgroups of patients, separately for each *Plasmodium* sp.:

- Patients who had gametocytes prior to dosing within a treatment episode (Day 0 value)
- Patients who did not have gametocytes prior to dosing within a treatment episode but who developed gametocytes during the treatment episode.

The summaries will comprise

- The number and percentage of patients with gametocytes by time point.
- Descriptive statistics of the gametocyte count in µL; this will also be presented graphically over time.
- Descriptive statistics of the log 10 area under the curve (AUC) of the gametocyte count in µL.

Prior to dosing within an episode will be the Day 0 value. If the number of gametocytes is missing it will be assumed to be 0, if there is an entry of the corresponding asexual forms for the same time point. Time points as recorded in the CRFS will be used for summarisation.

The area under the curve (AUC) of gametocyte count per µL will be calculated per patient using the trapezoidal rule. Since the observation period of patients during the actual malaria episodes varied up to 63 days, a cutoff at Day 42 + 2 days will be applied for gametocytes analyses.

All gametocytes analyses will be done separately for each *Plasmodium* sp. AUC analyses will only be done for *P. falciparum* due to the small sample sizes for *P. malariae* and *P. ovale*.

Kaplan-Meier analysis of all *P. falciparum/P. ovale/P. malariae* recurrences

The risk of a recurrence of the baseline *P. falciparum/P. ovale/P. malariae* infection after initial clearance will be analysed by means of Kaplan-Meier estimates per treatment episode. This analysis will be based on crude data and will be done separately for each *Plasmodium* sp. at baseline of the respective episode.. Patients who developed a *P. falciparum/P. ovale/P. malariae* recurrence during the treatment episode, after baseline, will be considered to have the event on the day the *P. falciparum/P. ovale/P. malariae* recurrence is diagnosed. The following censoring rules will be applied:

The following censoring rules will be applied:

- Patients with an infection with another sp. than the one present at baseline will be censored on the day the infection was diagnosed.

- Patients who received a prohibited concomitant medication will be censored on the medication start day.
- Patients who did not receive a full course of study treatment will be censored on the day of last dose.
- Patients who completed the study or discontinued prematurely (e.g. were lost to follow-up) without any of the previous conditions will be censored on the day of the last available parasite count (= last day of follow-up with an available parasite count according to the study schedule).

If more than one censoring condition occurred, the day of the earlier was used.

Kaplan-Meier analyses of cure will be censored at Day 42 + 2 days since the observation period until Day 63 was only applied in one centre.

Kaplan Meier analysis of re-infection (new infection) with *P. falciparum*

The risk of a new infection with *P. falciparum* will be analysed by means of Kaplan-Meier estimates. This analysis will be based on PCR-corrected data. Patients who developed a new *P. falciparum* infection, as confirmed by PCR or patients with a *P. falciparum* infection and an indeterminate/ incomplete PCR result, during the treatment episode, after baseline, will be considered to have the event on the day the new *P. falciparum* infection was diagnosed. The following censoring rules will be applied:

- Patients who received a prohibited concomitant medication will be censored on the day the treatment started.
- Patients who did not receive a full course of study drug will be censored on the day of last drug intake.
- Patients who had a recrudescence of *P. falciparum* parasites will be censored on the day of the recrudescence.
- Patients with evidence of both recrudescence and new infection at the time of parasite recurrence will be considered as recrudescent.
- Patients who completed the study without any of the above will be censored on the day of the last available parasite count.
- Patients who had an infection with another sp. will be considered censored on the day of the infection.

If a patient had more than one of the above reasons for censoring the earliest time point will be used. The *P. falciparum* new infection rate will be analysed for the intent-to-treat (ITT) population for those patients who had a *P. falciparum* infection

Kaplan-Meier analysis of recrudescence of *P. falciparum*

The risk of a recrudescence of the baseline *P. falciparum* infection after initial clearance will be analysed by means of Kaplan-Meier estimates. This analysis will be based on PCR-corrected data. Patients who developed a *P. falciparum* recrudescence, as confirmed by PCR, during the treatment episode, after baseline, will be considered to have the event on the day the *P. falciparum* recrudescence is diagnosed. The following censoring rules will be applied:

- Patients who received a prohibited concomitant medication will be censored on the day the treatment started.
- Patients who did not receive a full course of study drug will be censored on the day of last drug intake.
- Patients who had a new infection confirmed by PCR or a negative PCR result will be censored on the day of the new infection.
- Patients who completed the study or discontinued prematurely (e.g. were lost to follow-up) without any of the above will be censored on the day of the last available parasite count.

If a patient had more than one of the above reasons for censoring the earliest will be used. The *P. falciparum* recrudescence rate will be analysed for the ITT population.

Time until second infection and time between infections

The time between the first and the second uncomplicated malaria episodes and the time between each two uncomplicated malaria episodes will be summarised with descriptive statistics.

9. Exposure to study drug

The number and percentage of patients who received 1, 2, 3 etc. treatment episodes with study drug will be summarised by treatment group, together with the number of days between the first and the second, the second and the third etc. treatment episodes, as well as the average number of days between each two treatment episodes per patient. Days between treatment periods will be calculated as start date of second episode minus start date of first episode plus 1 etc.

The number and percentage of patients who received study drug as tablets or paediatric formulation (sachets / granules for PA and dispersible tablets for AL) per treatment episode will be presented.

Per treatment episode the following will be summarised:

- Number and percentage of patients who received one, two, three, or four doses of PA, ASAQ or DHA-PQP, or one, two, three, four, five, six, seven doses of AL. For vomited doses that were repeated the sum of both doses will be used.
- For patients in the PA, ASAQ or DHA-PQP group: Number and percentage of patients who vomited the first dose, the second dose, or the third dose.
- For patients in the AL group: Number and percentage of patients who vomited the first dose, the second dose, the third dose, the fourth dose, the fifth dose, or the sixth dose.
- Number and percentage of patients who received a repeated dose for the first dose and who vomited the repeated first dose.

The total amount of dose of study drug administered expressed in mg/kg body weight, separately for each drug's single components artesunate and pyronaridine tetraphosphate, artemether and lumefantrine, artesunate and amodiaquine, dihydroartemisinin and piperaquine. To calculate this, the total number of sachets/tablets taken by a patient will be multiplied by the strength and divided by the patient's body weight at baseline. For vomited doses that were repeated both the original and the repeated dose will be used.

10. Safety analysis

10.1 Adverse events

All adverse events (AEs) that were entered into the database will be coded using the most recent version of MedDRA dictionary for summarisation (V19.0). They will be attributed to the treatment episode when they occurred based on their start date. All AEs which started after the first dose of the first treatment episode but before the first dose of the second treatment episode, as recorded in the CRF, will be counted for the first, etc.

The following AE summaries will be generated by treatment group and by episode.

- An overview of the number and percentage of patients with
  - any AE
  - any serious AE
  - any severe or life-threatening AE
  - any AE considered to be related to study drug, whereby related will be defined as possible, probable, definite, or missing relationship, as assessed by the investigator. If the relationship to study medication is missing the worst case will be assumed, i.e. such AEs will also be considered study drug related.
  - any serious AE considered to be related to study drug
  - any AE leading to death
  - any AE leading to death considered to be related to study drug

- Number and percentage of patients with AEs by MedDRA primary system organ class and preferred term by treatment group and episode
- Number and percentage of patients with study drug related AEs (defined as possible, probable, definite or missing relationship to study drug) by MedDRA primary system organ class and preferred term by treatment group and episode
- Number and percentage of patients with serious AEs by MedDRA primary system organ class and preferred term by treatment group and episode
- Number and percentage of patients with AEs by MedDRA primary system organ class, preferred term and maximal severity, by treatment group and episode
- Number and percentage of patients with hepatotoxicity related adverse events, based on the Standard MedDRA Query (SMQ) narrow search "Drug-related hepatic disorders" (AEs of special interest).

Listings of all AEs as well as of all serious AEs will be provided. The treatment episode will be indicated on these listings. AEs and SAEs that occurred during complicated (severe) malaria episodes which were not treated with study drug will be included in the listings and flagged accordingly.

10.2 Clinical laboratory data

Clinical laboratory data (AST, ALT, total bilirubin, direct bilirubin, if total bilirubin is abnormal, alkaline phosphatase, serum creatinine, haemoglobin, platelet count, white blood count, neutrophils, lymphocytes, eosinophils) will be summarised by treatment episode and time point, including changes from Day 0 (pre-dose of each episode) with the number of observations, mean, standard deviation, median, quartiles, minimum and maximum.

If necessary, i.e., if values are collected in different units at different sites, values will be converted to SI units.

To evaluate potential anaemia, incidence rates of patients having a haemoglobin change from baseline:

≥0 g/dL, -2 - < 0 g/dL, or < -2 g/dL will be summarised by episode for each time point.

Incidence rates of liver enzyme abnormalities will be summarised by time point and for the worst (highest) value per episode based on the following event criteria (note that criteria are not mutually exclusive):

Parameter	Criterion
ALT	≤1.5 ULN, >1.5 ULN and ≤3 x ULN
	>3xULN; >5xULN; >10xULN
AST	≤1.5 ULN, >1.5 ULN and ≤3 x ULN
	>3xULN; >5xULN; >10xULN
ALT or AST	>3xULN; >5xULN; >10xULN
Total bilirubin (TBL)	>1.5xULN, >2xULN, >3xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN (Hy's Law)

ULN=upper limit of normal range of the local laboratory.

For a combined criterion to be fulfilled all criteria have to be fulfilled at the same time point.

This summary will also be provided for the defined subgroups.

Shift tables of the above categories at Day 0 of each treatment episode versus the worst post baseline value will be generated, also by for the subgroups.

The following graphical displays of liver function test data will be generated:

Comparison between treatment groups and between first and subsequent dosing using scatter plots of the peak total bilirubin value versus the peak ALT/AST values (expressed relative to the upper limit of normal) from Day 3 until Day 28 and from Day 7 until Day 28 of each episode (E-Dish graphs).

Scatter plots for ALT, total bilirubin showing individual data by episode and day (y axis will present value, x-axis will present Day 0, 3, 7 and 28 of each episode side-by-side) – separately for treatment groups.

10.3 Other data related to safety

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate) will be summarised by treatment episode and time point, including changes from Day 0 (pre-dose of each episode) with the number of observations, mean, standard deviation, median, quartiles, minimum and maximum. Vital signs measured in any position (sitting, supine, standing) will be combined for the summary tables.

ECG data from the central reading (QT, QTc (both Fridericia and Bazett correction), RR, PR, QRs intervals, heart rate) will be summarised by treatment episode and time point, including changes from Day 0 (pre-dose of each episode) with the number of observations, mean, standard deviation, median, quartiles, minimum and maximum.

Potential QTc prolongations with be evaluated by tabulating for each treatment episode the changes from pre dose (Day 0) ECG to worst (highest post dosing value) in categories (<=0 msec (no change, decrease), >0 - < 30 msec, 30 – 60 msec, > 60 msec). Further, events of prolonged absolute post dose QTc values (QTc > 450 msec, > 480 msec, > 500 msec) will be summarised. These tabulations will be presented for QTc calculated based on Bazett's and Fridericia's formulae. A listing of all QTc values for patients with an increase from Day 0 >30 msec or with a notable QTc value will be provided. Potential QTc prolongation incidence rates will further be tabulated for the subgroups.

11. Interim analyses/substudy analyses

The interim/substudy analyses performed for this study are described in separate SAPs which are included here. These analyses will be repeated on the finally locked database and will be included in the final CSR as appendices with the following changes:

- In the original substudy analyses PA was compared only with AL. For this final analysis they will also include the ASAQ comparator, as already done in the 2015 update.
- Since ASAQ data are included, the primary randomised efficacy population will be omitted since this analysis originally excluded patients from sites using ASAQ as comparator. This is not applicable anymore.
- The repeat dosing analyses will not be repeated for the sub population of patients receiving all repeat doses >90 days after preceding dose.
- Hepatotoxicity tables based on standard MedDRA queries will be removed.

final_sap_wanecam_
repeat_dose_substu

sap_wanecam_pyra
max_granules_final_

12. Blind review of data and planned analyses

The list of patients excluded from the EE population will be reviewed blinded by the medical reviewers and agreed upon prior to the analysis.

13. List of tables and figures

Please see Section 15.

14. List of data listings and statistical tabulations

Please see Section 15.

15. Table shells

Table 14.1.1 Enrolment of patients by country and centre
Overall safety population

Patients randomised	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Artesunate amodiaquine n (%)	DHA piperaquine n (%)	Total n (%)
Overall	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
Mali	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Bougoula	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Kolle	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Sotuba	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Guinea	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Mafrinyah	xxx (xx.x)	0 (0.0)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Burkina Faso	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Bobo	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Ouaga	xxx (xx.x)	0 (0.0)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

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

Table 14.1.2.1 Patient disposition and exposure
Overall safety population

	Pyronaridine artesunate	Artemether lumefantrine	Artesunate amodiaquine	DHA piperaquine	Total
Patients randomised	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
Patients treated (at least one dose) *					
1 episode	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
2 episodes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
3 episodes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
etc.					
Patients not re-treated for liver reasons	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Patients who completed study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Withdrawn from study prematurely	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
During active treatment period	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
During post-treatment follow-up	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other time point	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reason for withdrawal					
Treatment failure	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Death	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Protocol violation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lost to follow-up	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Withdrawal of consent	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Pregnancy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Study terminated by Sponsor	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

* Uncomplicated malaria episodes only.
Note: Percentages are based on the number of randomised patients.

Table 14.1.2.2 Patient disposition and exposure, by country
Overall safety population

Programming note: Same layout as Table 14.1.2.1. Present one page per country.

Table 14.1.2.3 Patient disposition and exposure, by age category
Overall safety population

Programming note: Same layout as Table 14.1.6.1. Present one page per age category.

Table 14.1.2.4 Patient disposition and exposure, by body weight category
Overall safety population

Programming note: Same layout as Table 14.1.6.1. Present one page per body weight category.

Table 14.1.3 Summary of analysis populations and reasons for exclusion from population

Treatment episode 1

Population	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Artesunate amodiaquine n (%)	DHA piperaquine n (%)	Total n (%)
Overall safety population	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
Intent-to-treat population	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
Day 28 efficacy evaluable population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Total excluded	xx (xx.x)	xx (xx.x)	xx (xx.x	xx (xx.x	xx (xx.x
Reason x	xx (xx.x)	NA	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc.					
etc.					

Note: Percentages are based on the number of randomised patients.
More than one reason for exclusion per patient and episode possible.

Table 14.1.4.1 Demographic characteristics
Overall safety population
(Page 1 of 3)

Variable/ Statistic/Category	Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)	Total (N=xxx)
Gender, n (%)					
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Age (years)					
Available observations	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
Standard deviation	x.xx	x.xx	x.xx	x.xx	x.xx
Minimum	xx	xx	xx	xx	xx
Q1	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx
Q3	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx
Age category, n (%)					
<18 years					
<=6 months	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>6 months – <1 year	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=1-<3 years	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=3-<6 years	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=6-<18 years	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=18 years	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Ethnicity group, n (%)					
Bamanan	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Bozo	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
etc.	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Missing values were not included in the calculation of percentages.

Table 14.1.4.1 Demographic characteristics
Overall safety population
(Page 2 of 3)

Variable/ Statistic/Category	Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)	Total (N=xxx)
Height (cm)					
Available observations	xxx	xxx	xxx	xxx	xxx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Standard deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xxx	xxx	xxx	xxx	xxx
Q1	xxx	xxx	xxx	xxx	xxx
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Q3	xxx	xxx	xxx	xxx	xxx
Maximum	xxx	xxx	xxx	xxx	xxx
Body weight (kg)					
Available observations	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
Standard deviation	x.xx	x.xx	x.xx	x.xx	x.xx
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x

Missing values were not included in the calculation of percentages.

Table 14.1.4.1 Demographic characteristics
Overall safety population
(Page 3 of 3)

Variable/ Statistic/Category	Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)	Total (N=xxx)
Body weight category, n (%)					
<20 kg	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=20 kg	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<10 kg	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=10 kg	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Body mass index (kg/m**2)					
Available observations	xxx	xxx	xxx	xxx	xxx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Standard deviation	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Q1	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Q3	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x

Missing values were not included in the calculation of percentages.

Table 14.1.4.2 Demographic characteristics
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.1.4.1.

Table 14.1.4.3 Demographic characteristics
Day 42 efficacy evaluable population

Programming note: Same layout as Table 14.1.4.1.

Table 14.1.4.4 Demographic characteristics, by country
Overall safety population

Programming note: Same layout as Table 14.1.4.1. Present one page per country.

Table 14.1.4.5 Demographic characteristics, by age category
Overall safety population

Programming note: Same layout as Table 14.1.4.1. Present one page per age category.

Table 14.1.4.6 Demographic characteristics, by body weight category
Overall safety population

Programming note: Same layout as Table 14.1.4.1. Present one page per body weight category.

Table 14.1.5.1 Baseline counts of *Plasmodium* sp. and baseline body temperature
Overall safety population

Variable/ Statistic/Category	Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)	Total (N=xxx)
Number (%) of patients at Day 0 of first episode who have					
P. falciparum asexual forms	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
P. falciparum gametocytes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
P. ovale asexual forms	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
P. ovale gametocytes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
P. malariae asexual forms	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
P. malariae gametocytes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
P. falciparum asexual forms at Day 0 of first episode (/uL)					
Available observations	xxx	xxx	xxx	xxx	xxx
Geometric mean *	xxxx.x	xxxx.x	xxxx.x	xxxx.x	xxxx.x
Mean	xxxx.x	xxxx.x	xxxx.x	xxxx.x	xxxx.x
Standard deviation	xxxx.x	xxxx.x	xxxx.x	xxxx.x	xxxx.x
Minimum	xxxx.x	xxxx.x	xxxx.x	xxxx.x	xxxx.x
Q1	xxxx.x	xxxx.x	xxxx.x	xxxx.x	xxxx.x
Median	xxxx.x	xxxx.x	xxxx.x	xxxx.x	xxxx.x
Q3	xxxx.x	xxxx.x	xxxx.x	xxxx.x	xxxx.x
Maximum	xxxx.x	xxxx.x	xxxx.x	xxxx.x	xxxx.x

Baseline refers to baseline of treatment episode 1.
* Geometric mean was only calculated if all counts were >0.

Variable/ Statistic/Category	Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)	Total (N=xxx)
Body temperature, n (%)					
No fever	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Fever	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Descriptive statistics (°C)					
Available observations	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
Standard deviation	x.xx	x.xx	x.xx	x.xx	x.xx
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x

Baseline refers to baseline of treatment episode 1.
* Geometric mean was only calculated if all counts were >0.

Table 14.1.5.2 Baseline counts of *Plasmodium* sp. and baseline body temperature
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.1.5.1.

Table 14.1.5.3 Baseline counts of *Plasmodium* sp. and baseline body temperature
Day 42 efficacy evaluable population

Programming note: Same layout as Table 14.1.5.1.

Table 14.1.5.4 Baseline counts of *Plasmodium* sp. and baseline body temperature, by country
Overall safety population

Programming note: Same layout as Table 14.1.5.1.

Table 14.1.5.5 Baseline counts of *Plasmodium* sp. and baseline body temperature, by age category
Overall safety population

Programming note: Same layout as Table 14.1.5.1.

Table 14.1.5.6 Baseline counts of *Plasmodium* sp. and baseline body temperature, by body weight category
Overall safety population

Programming note: Same layout as Table 14.1.5.1.

Table 14.2.1.1 Incidence rate of malaria episodes
Intent-to-treat population

	Pyronaridine artesunate	Artemether lumefantrine	Artesunate amodiaquine	DHA piperaquine
Number of malaria episodes in 2-year period				
Available observations	xxx	xxx	xxx	xxx
Mean	x.xx	x.xx	x.xx	x.xx
Standard deviation	x.xxx	x.xxx	x.xxx	x.xxx
Minimum	x	x	x	x
Q1	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Q3	x.xx	x.xx	x.xx	x.xx
Maximum	xx	xx	xx	xx
Incidence rate per 2 years				
Available observations	xxx	xxx	xxx	xxx
Mean	x.xx	x.xx	x.xx	x.xx
Standard deviation	x.xxx	x.xxx	x.xxx	x.xxx
Minimum	x.xx	x.xx	x.xx	x.xx
Q1	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Q3	x.xx	x.xx	x.xx	x.xx
Maximum	x.xx	x.xx	x.xx	x.xx

Incidence rate per two years is calculated as number of episodes/total observation time in days*730.

Table 14.2.1.2 Poisson regression results of incidence rate of malaria episodes
Intent-to-treat population

Treatment group comparison	Mean estimate of ratio	95% CI
AL vs PA	x.xx	x.xx - x.xx
ASAQ vs PA	x.xx	x.xx - x.xx
AL vs DHA-PQP	x.xx	x.xx - x.xx
ASAQ vs DHA-PQP	x.xx	x.xx - x.xx

Non-inferiority according to protocol definition can be assumed if the lower limit of the 95% confidence interval is greater than 0.8.

Table 14.2.1.3 Incidence rate of malaria episodes, by country
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.1. Present one page per subgroup.

Table 14.2.1.4 Incidence rate of malaria episodes, by age category
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.1. Present one page per subgroup.

Table 14.2.1.5 Incidence rate of malaria episodes, by body weight category
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.1. Present one page per subgroup.

Table 14.2.1.6 Day 28 crude *P. falciparum* ACPR rate by treatment episode
Intent-to-treat population

Treatment episode	Statistic	Pyronaridine artesunate	Artemether lumefantrine	Artesunate amodiaquine	DHA piperaquine
1	Available observations	xxx	xxx	xxx	xxx
	Number (%) of patients with ACPR	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	95% confidence interval (Pearson Clopper)	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
	Number (%) of treatment failures	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Early treatment failure	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Late clinical failure	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Late parasitological failure	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Rescue med/unknown (missing data)#	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	Available observations	xxx	xxx	xxx	xxx
	Number (%) of patients with ACPR	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	95% confidence interval (Pearson Clopper)	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
	Number (%) of treatment failures	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Reasons for treatment failure				
	Early treatment failure	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Late clinical failure	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Late parasitological failure	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Rescue med/unknown (missing data)#	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc.					

Patients with no *P. falciparum* asexual forms at Day 0 are not taken into account for cure calculation.
Includes patients with missing data, or who received rescue medication due to vomiting of study drug.

Table 14.2.1.7 Day 28 PCR-corrected *P. falciparum* ACPR rate by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.6.

Table 14.2.1.8 Day 42 crude *P. falciparum* ACPR rate by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.6.

Table 14.2.1.9 Day 42 PCR-corrected *P. falciparum* ACPR rate by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.6.

Table 14.2.1.10 Day 28 crude *P. falciparum* ACPR rate by treatment episode
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.1.6.

Table 14.2.1.11 Day 28 PCR-corrected *P. falciparum* ACPR rate by treatment episode
Day 28 efficacy evaluable population (PCR)

Programming note: Same layout as Table 14.2.1.6.

Table 14.2.1.12 Day 42 crude *P. falciparum* ACPR rate by treatment episode
Day 42 efficacy evaluable population

Programming note: Same layout as Table 14.2.1.6.

Table 14.2.1.13 Day 42 PCR-corrected *P. falciparum* ACPR rate by treatment episode
Day 42 efficacy evaluable population (PCR)

Programming note: Same layout as Table 14.2.1.6.

Table 14.2.1.14 Day 28 crude *P. falciparum* ACPR rate by treatment episode and country
Intent-to-treat population
Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.15 Day 28 PCR-corrected *P. falciparum* ACPR rate by treatment episode and country
Intent-to-treat population
Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.16 Day 42 crude *P. falciparum* ACPR rate by treatment episode and country
Intent-to-treat population
Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.17 Day 42 PCR-corrected *P. falciparum* ACPR rate by treatment episode and country
Intent-to-treat population
Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.18 Day 28 crude *P. falciparum* ACPR rate by treatment episode and age category
Intent-to-treat population
Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.19 Day 28 PCR-corrected *P. falciparum* ACPR rate by treatment episode and age category
Intent-to-treat population
Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.20 Day 42 crude *P. falciparum* ACPR rate by treatment episode and age category
Intent-to-treat population
Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.21 Day 42 PCR-corrected *P. falciparum* ACPR rate by treatment episode and age category
Intent-to-treat population
Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.22 Day 28 crude *P. falciparum* ACPR rate by treatment episode and body weight category
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.23 Day 28 PCR-corrected *P. falciparum* ACPR rate by treatment episode and body weight category
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.24 Day 42 crude *P. falciparum* ACPR rate by treatment episode and body weight category
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.1.25 Day 42 PCR-corrected *P. falciparum* ACPR rate by treatment episode and body weight category
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.6 with a separate page for each subgroup.

Table 14.2.2.1 GEE estimates of crude and PCR corrected *P. falciparum* ACPR
Intent-to-treat population
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		Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)
Crude ACPR					
Day 28	Number of patients	xxx	xxx	xxx	xxx
	Total number of episodes	xxx	xxx	xxx	xxx
	ACPR estimate	xx.x	xx.x	xx.x	xx.x
	95% confidence interval	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Day 42	Number of patients	xxx	xxx	xxx	xxx
	Total number of episodes	xxx	xxx	xxx	xxx
	ACPR estimate	xx.x	xx.x	xx.x	xx.x
	95% confidence interval	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
PCR-corrected ACPR					
Day 28	Number of patients	xxx	xxx	xxx	xxx
	Total number of episodes	xxx	xxx	xxx	xxx
	ACPR estimate	xx.x	xx.x	xx.x	xx.x
	95% confidence interval	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Day 42	Number of patients	xxx	xxx	xxx	xxx
	Total number of episodes	xxx	xxx	xxx	xxx
	ACPR estimate	xx.x	xx.x	xx.x	xx.x
	95% confidence interval	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)

Results estimated from GEE model with treatment group as fixed effect and patient as random effect.

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	Treatment group comparison	Mean estimate of difference	95% CI
Crude ACPR			
Day 28	PA vs AL	x.xx	x.xx - x.xx
	PA vs ASAQ	x.xx	x.xx - x.xx
	DHA-PQP vs AL	x.xx	x.xx - x.xx
	DHA-PQP vs ASAQ	x.xx	x.xx - x.xx
Day 42	PA vs AL	x.xx	x.xx - x.xx
	PA vs ASAQ	x.xx	x.xx - x.xx
	DHA-PQP vs AL	x.xx	x.xx - x.xx
	DHA-PQP vs ASAQ	x.xx	x.xx - x.xx
PCR corrected ACPR			
Day 28	PA vs AL	x.xx	x.xx - x.xx
	PA vs ASAQ	x.xx	x.xx - x.xx
	DHA-PQP vs AL	x.xx	x.xx - x.xx
	DHA-PQP vs ASAQ	x.xx	x.xx - x.xx
Day 42	PA vs AL	x.xx	x.xx - x.xx
	PA vs ASAQ	x.xx	x.xx - x.xx
	DHA-PQP vs AL	x.xx	x.xx - x.xx
	DHA-PQP vs ASAQ	x.xx	x.xx - x.xx

Results estimated from GEE model with treatment group as fixed effect and patient as random effect.

Table 14.2.2.2 GEE estimates of crude and PCR corrected *P. falciparum* ACPR
Efficacy evaluable population

Programming note: Same layout as Table 14.2.2.1.

Table 14.2.3.1 Day 28 crude *P. malariae* ACPR rate by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.5.

Table 14.2.3.2 Day 42 crude *P. malariae* ACPR rate by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.5.

Table 14.2.3.3 Day 28 crude *P. malariae* ACPR rate by treatment episode
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.1.5.

Table 14.2.3.4 Day 42 crude *P. malariae* ACPR rate by treatment episode
Day 42 efficacy evaluable population

Programming note: Same layout as Table 14.2.1.5.

Table 14.2.3.5 Day 28 crude *P. ovale* ACPR rate by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.5.

Table 14.2.3.6 Day 42 crude *P. ovale* ACPR rate by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.1.5.

Table 14.2.3.7 Day 28 crude *P. ovale* ACPR rate by treatment episode
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.1.5.

Table 14.2.3.8 Day 42 crude *P. ovale* ACPR rate by treatment episode
Day 42 efficacy evaluable population

Programming note: Same layout as Table 14.2.1.5.

Table 14.2.3.9 Summary of time between all malaria episodes in days
Intent-to-treat population

	Pyronaridine artesunate	Artemether lumefantrine	Artesunate amodiaquine	DHA piperaquine
Episode 1 until Episode 2				
Number of patients	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x
Standard deviation	x.xx	x.xx	x.xx	x.xx
Minimum	xx	xx	xx	xx
Q1	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx
Q3	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx
n (%)				
28-60 days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
61-90 days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>90 days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<=30 days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<=60 days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<=90 days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
continue with Episode 2 until Episode 3 and median between episodes etc.				

Table 14.2.3.10 Summary of time between all malaria episodes in days, by country
Intent-to-treat population

Programming note: Same layout as Table 14.2.3.9 with a separate page for each subgroup.

Table 14.2.3.11 Summary of time between all malaria episodes in days, by age category
Intent-to-treat population

Programming note: Same layout as Table 14.2.3.9 with a separate page for each subgroup.

Table 14.2.3.12 Summary of time between all malaria episodes in days, by body weight category
Intent-to-treat population

Programming note: Same layout as Table 14.2.3.9 with a separate page for each subgroup.

Table 14.2.4.1 Kaplan-Meier estimates of time until *P. falciparum* clearance in hours, by treatment episode
Intent-to-treat population

Treatment episode 1

Statistic	Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)
Available observations	xxx	xxx	xxx	xxx
Number of patients with *P. falciparum* clearance	xxx	xxx	xxx	xxx
Number of censored observations	xxx	xxx	xxx	xxx
Clearance time (hours)				
25th percentile (Two-sided 95% CI)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
Median (Two-sided 95% CI)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
75th percentile (Two sided 95% CI)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
P. falciparum clearance achieved at				
24 hours after first dose				
Rate (%)	xx.x	xx.x	xx.x	xx.x
Two-sided 95% confidence interval	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
48 hours after first dose				
Rate (%)	xx.x	xx.x	xx.x	xx.x
Two-sided 95% confidence interval	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
72 hours after first dose				
Rate (%)	xx.x	xx.x	xx.x	xx.x
Two-sided 95% confidence interval	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x

Programming note: Continue with further treatment episodes

Table 14.2.4.2 Kaplan-Meier estimates of time until *P. falciparum* clearance in hours, by treatment episode
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.4.1.

Table 14.2.4.3 Kaplan-Meier estimates of time until *P. falciparum* clearance in hours, by treatment episode and body weight category
Intent-to-treat population

Programming note: Same layout as Table 14.2.4.1.

Table 14.2.4.4 Kaplan-Meier estimates of time until *P. malariae* clearance in hours, by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.4.1.

Table 14.2.4.5 Kaplan-Meier estimates of time until *P. malariae* clearance in hours, by treatment episode
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.4.1.

Table 14.2.4.6 Kaplan-Meier estimates of time until *P. ovale* clearance in hours, by treatment episode
Intent-to-treat population

Programming note: Same layout as Table 14.2.4.1.

Table 14.2.4.7 Kaplan-Meier estimates of time until *P. ovale* clearance in hours, by treatment episode
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.4.1.

Table 14.2.5.1 Number (%) of patients with no fever, by *Plasmodium* sp., treatment episode, and time point
Intent-to-treat population

Patients with P. falciparum

Treatment episode	Time point	Pyronaridine artesunate n / total (%)	Artemether lumefantrine n / total (%)	Artesunate amodiaquine n / total (%)	DHA piperaquine n / total (%)
1	Day 0	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 1	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 2	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 3	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 7	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 14	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 28	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 35	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 42	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
2	Day 0	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 1	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 2	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 3	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 7	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
etc.					

Note: Total is the number of patients with an available observation on the respective time point.
Programming note: Continue with other sp.

Table 14.2.5.2 Number (%) of patients with no fever, by *Plasmodium* sp., treatment episode and time point
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.5.1.

Table 14.2.6.1 Number (%) of patients with *P. falciparum* gametocytes, by treatment episode and time point
Intent-to-treat population

Treatment episode	Time point	Pyronaridine artesunate n / total (%)	Artemether lumefantrine n / total (%)	Artesunate amodiaquine n / total (%)	DHA piperaquine n / total (%)
1	Day 0	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Post-baseline				
	12 hours	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	24 hours	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	36 hours	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	48 hours	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	60 hours	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	72 hours	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 7	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Day 14				
2	etc.	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	Any post baseline	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)

etc.

Note: Total is the number of patients with an available observation on the respective time point.

Table 14.2.6.2 Number (%) of patients with *P. falciparum* gametocytes, by treatment episode, time point and baseline gametocyte carriage
Intent-to-treat population

Treatment episode 1

	With *P. falciparum* gametocytes at Day 0 of episode			
	Pyronaridine artesunate n / Total (%)	Artemether lumefantrine n / Total (%)	Artesunate amodiaquine n / Total (%)	DHA piperaquine n / Total (%)
Day 0	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Post-baseline				
12 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
24 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
36 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
48 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
60 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
72 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Day 7	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Day 14	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
etc.	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Any post baseline	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)

Note: Total is the number of patients with an available observation on the respective time point.

	Without *P. falciparum* gametocytes at Day 0 of episode but subsequently			
	Pyronaridine artesunate n / Total (%)	Artemether lumefantrine n / Total (%)	Artesunate amodiaquine n / Total (%)	DHA piperaquine n / Total (%)
Day 0	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Post-baseline				
12 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
24 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
36 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
48 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
60 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
72 hours	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Day 7	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Day 14	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
etc.	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Any post baseline	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)

Note: Total is the number of patients with an available observation on the respective time point.

Table 14.2.6.3 Number (%) of patients with *P. falciparum* gametocytes, by treatment episode and time point
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.6.1.

Table 14.2.6.4 Number (%) of patients with *P. falciparum* gametocytes, by treatment episode, time point and baseline gametocyte carriage
Day 28 efficacy evaluable population

Programming note: Same layout as Table 14.2.6.2.

Table 14.2.6.5 Log10 area under the curve for *P. falciparum* gametocytes, by episode
Intent-to-treat population

Treatment episode	Variable/ Statistic	With P. *falciparum* gametocytes at Day 0 of episode: Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)
1	Log10 area under the curve				
	Available observations	xxx	xxx	xxx	xxx
	Mean	x.xxx	x.xxx	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx	x.xxxx	x.xxxx
	Minimum	x.xxx	x.xxx	x.xxx	x.xxx
	Q1	x.xxx	x.xxx	x.xxx	x.xxx
	Median	x.xxx	x.xxx	x.xxx	x.xxx
	Q3	x.xxx	x.xxx	x.xxx	x.xxx
	Maximum	x.xxx	x.xxx	x.xxx	x.xxx
2	Log10 area under the curve				
	Available observations	xxx	xxx	xxx	xxx
	Mean	x.xxx	x.xxx	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx	x.xxxx	x.xxxx
	Minimum	x.xxx	x.xxx	x.xxx	x.xxx
	Q1	x.xxx	x.xxx	x.xxx	x.xxx
	Median	x.xxx	x.xxx	x.xxx	x.xxx
	Q3	x.xxx	x.xxx	x.xxx	x.xxx
	Maximum	x.xxx	x.xxx	x.xxx	x.xxx
etc.					

Log10 AUCs for P. falciparum gametocytes are calculated in count*day/uL based on a Log10 transformation.

Treatment episode	Variable/ Statistic	Without *P. falciparum* gametocytes at Day 0 of episode but subsequently			
		Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)
1	Log10 area under the curve				
	Available observations	xxx	xxx	xxx	xxx
	Mean	x.xxx	x.xxx	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx	x.xxxx	x.xxxx
	Minimum	x.xxx	x.xxx	x.xxx	x.xxx
	Q1	x.xxx	x.xxx	x.xxx	x.xxx
	Median	x.xxx	x.xxx	x.xxx	x.xxx
	Q3	x.xxx	x.xxx	x.xxx	x.xxx
	Maximum	x.xxx	x.xxx	x.xxx	x.xxx
2	Log10 area under the curve				
	Available observations	xxx	xxx	xxx	xxx
	Mean	x.xxx	x.xxx	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx	x.xxxx	x.xxxx
	Minimum	x.xxx	x.xxx	x.xxx	x.xxx
	Q1	x.xxx	x.xxx	x.xxx	x.xxx
	Median	x.xxx	x.xxx	x.xxx	x.xxx
	Q3	x.xxx	x.xxx	x.xxx	x.xxx
	Maximum	x.xxx	x.xxx	x.xxx	x.xxx
etc.					

Log10 AUCs for P. falciparum gametocytes are calculated in count*day/uL based on a Log10 transformation.

Table 14.2.6.6 Log10 area under the curve for *P. falciparum* gametocytes, by episode
Day 28 evaluable efficacy population

Programming note: Same layout as Table 14.2.6.5.

Table 14.2.6.7 Number (%) of patients with *P. malariae* gametocytes, by treatment episode and time point
Intent-to-treat population

Programming note: Same layout as Table 14.2.6.1.

Table 14.2.6.8 Number (%) of patients with *P. malariae* gametocytes, by treatment episode, time point and baseline gametocyte carriage
Intent-to-treat population

Programming note: Same layout as Table 14.2.6.2.

Table 14.2.6.9 Number (%) of patients with *P. ovale* gametocytes, by treatment episode and time point
Intent-to-treat population

Programming note: Same layout as Table 14.2.6.1.

Table 14.2.6.10 Number (%) of patients with *P. ovale* gametocytes, by treatment episode, time point and baseline gametocyte carriage
Intent-to-treat population

Programming note: Same layout as Table 14.2.6.2.

Table 14.3.1.1 Summary of drug formulation taken
Overall safety population

Treatment episode		Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Artesunate amodiaquine n (%)	DHA piperaquine n (%)
1	Number of patients dosed	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
	Tablets	NA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Paediatric formulation *	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
2	Number of patients dosed	xxx	xxx	xxx	xxx
	Tablets	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Paediatric formulation *	xxx (xx.x)	xxx (xx.x)	NA	NA
etc.					

* Sachets (granules) for PA and dispersible tablets for AL. Not applicable for the other two treatments.

Table 14.3.1.2 Study drug exposure, by treatment episode
Overall safety population

Treatment episode 1

Variable/ Category	Pyronaridine artesunate (N=xxx) n (%)	Artemether lumefantrine (N=xxx) n (%)	Artesunate amodiaquine (N=xxx) n (%)	DHA piperaquine (N=xxx) n (%)
Total number of doses taken *				
One	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Two	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Three	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Four	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Five	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Six	NA	xxx (xx.x)	NA	NA
Seven	NA	xxx (xx.x)	NA	NA
Eight	NA	xxx (xx.x)	NA	NA
Dose repeated				
Day 0 – Dose 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 0 – Dose 2	NA	xx (xx.x)	NA	NA
Day 1 – Dose 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .				
Dose vomited within 30 minutes				
Day 0 - Dose 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Repeated dose	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Day 0 - Dose 2	NA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Repeated dose	NA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
. . .				

NA = not applicable
* Original and repeat doses were taken into account.

Table 14.3.1.3 Study drug dosage, by treatment episode
Overall safety population

Treatment episode 1

Variable/ Statistic	Pyronaridine artesunate (N=xxx)	Artemether lumefantrine (N=xxx)	Artesunate amodiaquine (N=xxx)	DHA piperaquine (N=xxx)
mg/kg	Artesunate	Artemether	Artesunate	DHA
Available observations	xxx	xxx	xxx	xxx
Mean	x.xx	x.xx	x.xx	x.xx
SD	x.xxx	x.xxx	x.xxx	x.xxx
Minimum	x.xx	x.xx	x.xx	x.xx
Q1	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Q3	x.xx	x.xx	x.xx	x.xx
Maximum	x.xx	x.xx	x.xx	x.xx
mg/kg	Pyronaridine	Lumefantrine	Amodiaquine	Piperaquine
Available observations	xxx	xxx	xxx	xxx
Mean	x.xx	x.xx	x.xx	x.xx
SD	x.xxx	x.xxx	x.xxx	x.xxx
Minimum	x.xx	x.xx	x.xx	x.xx
Q1	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Q3	x.xx	x.xx	x.xx	x.xx
Maximum	x.xx	x.xx	x.xx	x.xx

Note: Original and repeat doses were taken into account.

Table 14.3.1.4 Summary of time between treatment episodes in days
Overall safety population

Programming note: Same layout as Table 14.2.3.9 for a different variable.

Table 14.3.1.1.1 Overview of adverse events, by treatment episode
Overall safety population

Treatment episode	Number (%) of patients with	Pyronaridine artesunate (N=xxx) n (%)	Artemether lumefantrine (N=xxx) n (%)	Artesunate amodiaquine (N=xxx) n (%)	DHA piperaquine (N=xxx) n (%)
1	Number of patients dosed	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
	Any adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any drug-related adverse event *	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any serious adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any serious drug-related adverse event *	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any severe or life-threatening adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any adverse event leading to death	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
2	Number of patients dosed	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
	Any adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any drug-related adverse event *	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any serious adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any serious drug-related adverse event *	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any severe or life-threatening adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Any adverse event leading to death	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
3 etc. 2+	etc.				

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

Table 14.3.1.1.2 Incidence of all adverse events by MedDRA primary system organ class and preferred term, by treatment episode Overall safety population

Treatment episode 1

Primary system organ class Preferred term	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Artesunate amodiaquine n (%)	DHA piperaquine n (%)
Patients dosed	xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
At least one adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Primary system organ class 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Primary system organ class 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
etc.				

A patient with more than one adverse event within a primary system organ class is counted only once for that class.

Programming note: continue with treatment episode 2, 3 etc.

Table 14.3.1.1.3 Incidence of adverse events considered to be study drug related, by MedDRA primary system organ class and preferred term, by treatment episode
Overall safety population

Programming note: Same layout as Table 14.3.1.2. Present only AEs that were considered to be study drug-related. No p-values.

Table 14.3.1.1.4 Incidence of serious adverse events, by MedDRA primary system organ class and preferred term, by treatment episode
Overall safety population

Programming note: Same layout as Table 14.3.1.2. Present serious AEs. No p-values.

Table 14.3.1.1.5 Incidence of serious adverse events considered to be study drug related, by MedDRA primary system organ class and preferred term, by treatment episode
Overall safety population

Programming note: Same layout as Table 14.3.1.2. Present serious AEs that were considered to be study drug related. No p-values.

Table 14.3.1.1.6 Incidence of all adverse events by MedDRA primary system organ class, preferred term, maximal severity and treatment episode
Overall safety population

Treatment episode 1

Primary system organ class	Preferred term	Maximal severity	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Artesunate amodiaquine n (%)	DHA piperaquine n (%)
Patients dosed			xxx (100.0)	xxx (100.0)	xxx (100.0)	xxx (100.0)
At least one AE	Total	Total	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Severe	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Primary SOC 1	Total	Total	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Preferred term 1	Total	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
etc.						

If a patient reported more than one adverse event within the same category, the worst severity was summarised.
A patient with more than one adverse event within a primary system organ class is counted only once for that class.

Table 14.3.1.1.7 Overview of adverse events, by treatment episode and country
Overall safety population

Programming note: same layout as Table 14.3.1.1 starting a new page for each country

Table 14.3.1.1.8 Incidence of all adverse events by MedDRA primary system organ class and preferred term, by treatment episode and country
Overall safety population

Programming note: same layout as Table 14.3.1.2 starting a new page for each country

Table 14.3.1.1.9 Overview of adverse events, by treatment episode and age category
Overall safety population

Programming note: same layout as Table 14.3.1.1 starting a new page for each age category

Table 14.3.1.1.10 Incidence of all adverse events by MedDRA primary system organ class and preferred term, by treatment episode and age category
Overall safety population

Programming note: same layout as Table 14.3.1.2 starting a new page for each age category

Table 14.3.1.1.11 Overview of adverse events, by treatment episode and body weight category
Overall safety population

Programming note: same layout as Table 14.3.1.1 starting a new page for each body weight category

Table 14.3.1.1.12 Incidence of all adverse events by MedDRA primary system organ class and preferred term, by treatment episode and age category
Overall safety population

Programming note: same layout as Table 14.3.1.2 starting a new page for each body weight category

Table 14.3.2.1 Summary of ALT values (U/L) by treatment episode, treatment and time point
Overall safety population

Treatment episode 1

	Time point	N	Mean	SD	Minimum	Q1	Median	Q3	Maximum
Pyronaridine artesunate (N=xxx)									
Raw values	Day 0	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 3	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 7	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 28	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Changes from Day 0	Day 3	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 7	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 28	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Artemether lumefantrine (N=xxx)									
Raw values	Day 0	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 3	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 7	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 28	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Changes from Day 0	Day 3	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 7	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Day 28	xxx	xx.x	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
etc.									

Programming note: continue with other treatment groups and other treatment episodes.

Table 14.3.2.2 Summary of AST values (U/L) by treatment episode, treatment and time point
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for AST

Table 14.3.2.3 Summary of total bilirubin values (mg/dL) by treatment episode, treatment and time point
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for total bilirubin

Table 14.3.2.4 Summary of alkaline phosphatase values (U/L) by treatment episode, treatment and time point
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for alkaline phosphatase

Table 14.3.2.5 Summary of serum creatinine values (mg/dL) by treatment episode, treatment and time point
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for serum creatinine

Table 14.3.2.6 Incidence of ALT values relative to the normal range, by treatment episode, treatment and time point
Overall safety population

Treatment episode 1

Time point		Pyronaridine artesunate (N=xxx) n / total (%)	Artemether lumefantrine (N=xxx) n / total (%)	Artesunate amodiaquine (N=xxx) n / total (%)	DHA piperaquine (N=xxx) n / total (%)
Day 0	ALT <=1.5 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >1.5 x ULN and <=3 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >3 x ULN and <=5 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >5 x ULN and <=10 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >10 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
Day 3	ALT <=1.5 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >1.5 x ULN and <=3 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >3 x ULN and <=5 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >5 x ULN and <=10 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >10 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
Day 7	...				
Day 28	...				
Highest value post Day 0 ...					

ULN = Upper limit of normal range

Programming note: continue with other episodes and episode 2+

Table 14.3.2.7 Incidence of AST values relative to the normal range, by treatment episode, treatment and time point
Overall safety population

Programming note: Same layout as Table 14.3.2.6 for AST

Table 14.3.2.8 Incidence of liver enzyme classifications, by treatment episode, treatment and time point
Overall safety population
(Page 1 of 1)

Treatment episode 1

Time point		Pyronaridine artesunate (N=xxx) n / total (%)	Artemether lumefantrine (N=xxx) n / total (%)	Artesunate amodiaquine (N=xxx) n / total (%)	DHA piperaquine (N=xxx) n / total (%)
Day 0	ALT >3 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >5 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT >10 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	AST >3 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	AST >5 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	AST >10 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT or AST >3 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT or AST >5 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	ALT or AST >10 x ULN	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)	xx / xxx (xx.x)
	TBIL >1.5 x ULN				
	TBIL >2 x ULN				
	TBIL >3 x ULN				
	Hy's law (ALT or AST >3 x ULN and TBIL >2 x ULN)				
Day 3					
Day 7	...				
Day 28	...				
Highest value post Day 0	...				

ULN = Upper limit of normal range
TBIL = total bilirubin
Programming note: continue with other episodes

Table 14.3.2.9 Shift table of ALT categories from Day 0 pre dose to the worst post dose value, by treatment episode and treatment
Overall safety population
(Page 1 of 1)

Treatment episode 1

		Number (%) of patients: Day 0					
Treatment		Total	<1.5 x ULN	>1.5-<=3 x ULN	>3-<=5 x ULN	>5-<=10 x ULN	>10 x ULN
Pyronaridine-artesunate	Total	xxx (100)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	<1.5 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>1.5-<=3 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>3-<=5 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>5-<=10 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>10 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Artemether-lumefantrine	Total	xxx (100)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	<1.5 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>1.5-<=3 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>3-<=5 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>5-<=10 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>10 x ULN	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

etc.

ULN = upper limit of normal range
Patients with a pre-dose and at least on post dose ALT value are included.

Programming note: continue with treatment groups artesunate-amodiaquine and DHA piperaquine and with other episodes and episode 2+

Table 14.3.2.10 Shift table of AST categories from Day 0 pre dose to the worst post dose value, by treatment episode and treatment
Overall safety population

Programming note: Same layout as Table 14.3.2.9 for AST

Table 14.3.2.11 Summary of haemoglobin values (g/dL) by treatment episode, treatment and time point
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for haemoglobin

Table 14.3.2.12 Summary of platelet values (103/mm**3) by treatment episode, treatment and time point**
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for platelets

Table 14.3.2.13 Summary of white blood cell count values (103/mm**3) by treatment episode, treatment and time point**
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for WBC

Table 14.3.2.14 Summary of absolute neutrophils (103/mm**3) by treatment episode, treatment and time point**
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for absolute neutrophils

Table 14.3.2.15 Summary of absolute lymphocytes (103/mm**3) by treatment episode, treatment and time point**
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for absolute lymphocytes

Table 14.3.2.16 Summary of absolute eosinophils (103/mm**3) by treatment episode, treatment and time point**
Overall safety population

Programming note: Same layout as Table 14.3.2.1 for absolute eosinophils

Table 14.3.2.17 Incidence of changes from baseline in haemoglobin
Overall safety population
(Page 1 of 1)

Treatment episode 1

Time point	Change from baseline	Pyronaridine artesunate (N=xxx) n (%)	Artemether lumefantrine (N=xxx) n (%)	Artesunate amodiaquine (N=xxx) n (%)	DHA piperaquine (N=xxx) n (%)
Day 3	Available observations	xxx (100)	xxx (100)	xxx (100)	xxx (100)
	< -2 g/dL (decrease >2 g/dL)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	-2 - <0 g/dL (decrease >0-2 g/dL)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	>=0 g/dL (increase or no change)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 7	Available observations	xxx (100)	xxx (100)	xxx (100)	xxx (100)
	< -2 g/dL (decrease >2 g/dL)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	-2 - <0 g/dL (decrease >0-2 g/dL)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	>=0 g/dL (increase or no change)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 28	Available observations	xxx (100)	xxx (100)	xxx (100)	xxx (100)
	< -2 g/dL (decrease >2 g/dL)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	-2 - <0 g/dL (decrease >0-2 g/dL)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	>=0 g/dL (increase or no change)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Percentages are based on the number of available observations at each time point.

Table 14.3.2.18 Incidence of ALT values relative to the normal range, by country, treatment episode, treatment and time point
Overall safety population

Programming note: same layout as table 14.3.2.6 starting a new page for each country

Table 14.3.2.19 Incidence of liver enzyme classifications, by treatment episode, treatment, time point and country
Overall safety population

Programming note: same layout as table 14.3.2.8 starting a new page for each country

Table 14.3.2.20 Shift table of ALT categories from Day 0 pre dose to the worst post dose value, by treatment episode, treatment and country
Overall safety population

Programming note: same layout as table 14.3.2.9 starting a new page for each country

Table 14.3.2.21 Incidence of ALT values relative to the normal range, by age category, treatment episode, treatment and time point
Overall safety population

Programming note: same layout as table 14.3.2.6 starting a new page for each age category

Table 14.3.2.22 Incidence of liver enzyme classifications, by treatment episode, treatment, time point and age category
Overall safety population

Programming note: same layout as table 14.3.2.8 starting a new page for each age category

Table 14.3.2.23 Shift table of ALT categories from Day 0 pre dose to the worst post dose value, by treatment episode, treatment and age category
Overall safety population

Programming note: same layout as table 14.3.2.9 starting a new page for each age category

Table 14.3.2.24 Incidence of ALT values relative to the normal range, by treatment episode, treatment, time point and body weight category
Overall safety population

Programming note: same layout as table 14.3.2.6 starting a new page for each body weight category

Table 14.3.2.25 Incidence of liver enzyme classifications, by treatment episode, treatment, time point and body weight category
Overall safety population

Programming note: same layout as table 14.3.2.8 starting a new page for each body weight category

Table 14.3.2.26 Shift table of ALT categories from Day 0 pre dose to the worst post dose value, by treatment episode, treatment and body weight category
Overall safety population

Programming note: same layout as table 14.3.2.9 starting a new page for each body weight category

Table 14.3.3.1 Summary of vital signs by treatment episode and treatment
Overall safety population
(Page 1 of n)

Parameter: Systolic blood pressure (mm Hg)
Treatment episode 1

	Time point	N	Mean	SD	Minimum	Q1	Median	Q3	Maximum
Pyronaridine artesunate (N=xxx)									
Raw values	Day 0	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 1	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 2	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 3	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 7	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 14	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 28	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 35	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 42	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 63	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
Changes from Day 0	Day 1	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 2	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 3	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 7	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 14	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 28	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 35	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 42	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 63	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx

Programming note: Continue with treatment groups artemether lumefantrine, artesunate amodiaquine, DHA piperaquine and further treatment episode. Vital signs diastolic blood pressure (mm Hg) and pulse (bpm) will follow on subsequent pages.

Table 14.3.3.2 Summary of ECG parameters by treatment episode and treatment, central ECG reading
Overall safety population
(Page 1 of n)

Parameter: PR interval (ms)
Treatment episode 1

	Time point	N	Mean	SD	Minimum	Q1	Median	Q3	Maximum
Pyronaridine artesunate (N=xxx)									
Raw values	Day 0	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 2	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 3	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 42	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
Changes from Day 0	Day 2	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 3	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 42	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
Artemether lumefantrine (N=xxx)									
Raw values	Day 0	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 2	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 3	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 42	xxx	xxx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
Changes from Day 0	Day 2	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 3	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx
	Day 42	xxx	xx.x	x.xx	xxx	xxx.x	xxx.x	xxx.x	xxx

etc.

Programming note: Continue with further treatment groups and treatment episodes and other ECG parameters: RR interval, QRS interval, QT interval, QTc interval (Bazett, Fridericia), heart rate

Table 14.3.3.3 Number (%) of patients with signal QTc values or signal QTc increases from Day 0 of actual episode, central ECG reading
Overall safety population

Treatment episode 1

	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Artesunate amodiaquine n (%)	DHA piperaquine n (%)
Patients dosed and ECG available	xxx	xxx	xxx	xxx
QTc based on Bazett's formula				
Increase between highest post dose value and Day 0	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<= 0 msec (decrease)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>0 - <30 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
30 – 60 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
> 60 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Day 0 missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any post dose QTc > 450 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any post dose QTc > 480 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any post dose QTc > 500 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
QTc based on Fridericia's formula				
Increase between highest post dose value and Day 0	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<= 0 msec (decrease)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>0 - <30 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
30 – 60 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
> 60 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Day 0 missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any post dose QTc > 450 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any post dose QTc > 480 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any post dose QTc > 500 msec	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Programming note: Continue with further treatment episodes

Table 14.3.3.4 Number (%) of patients with signal QTc values or signal QTc increases from Day 0 of actual episode, central ECG reading, by country
Overall safety population

Programming note: same layout as table 14.3.3.3 starting a new page for each body weight category

Table 14.3.3.5 Number (%) of patients with signal QTc values or signal QTc increases from Day 0 of actual episode, central ECG reading, by age category
Overall safety population

Programming note: same layout as table 14.3.3.3 starting a new page for each age category

Figure 14.2.2.1 **Kaplan-Meier estimates for time until *P. falciparum* recurrence**
Intent-to-treat population
(Page 1 of n)

Treatment episode 1

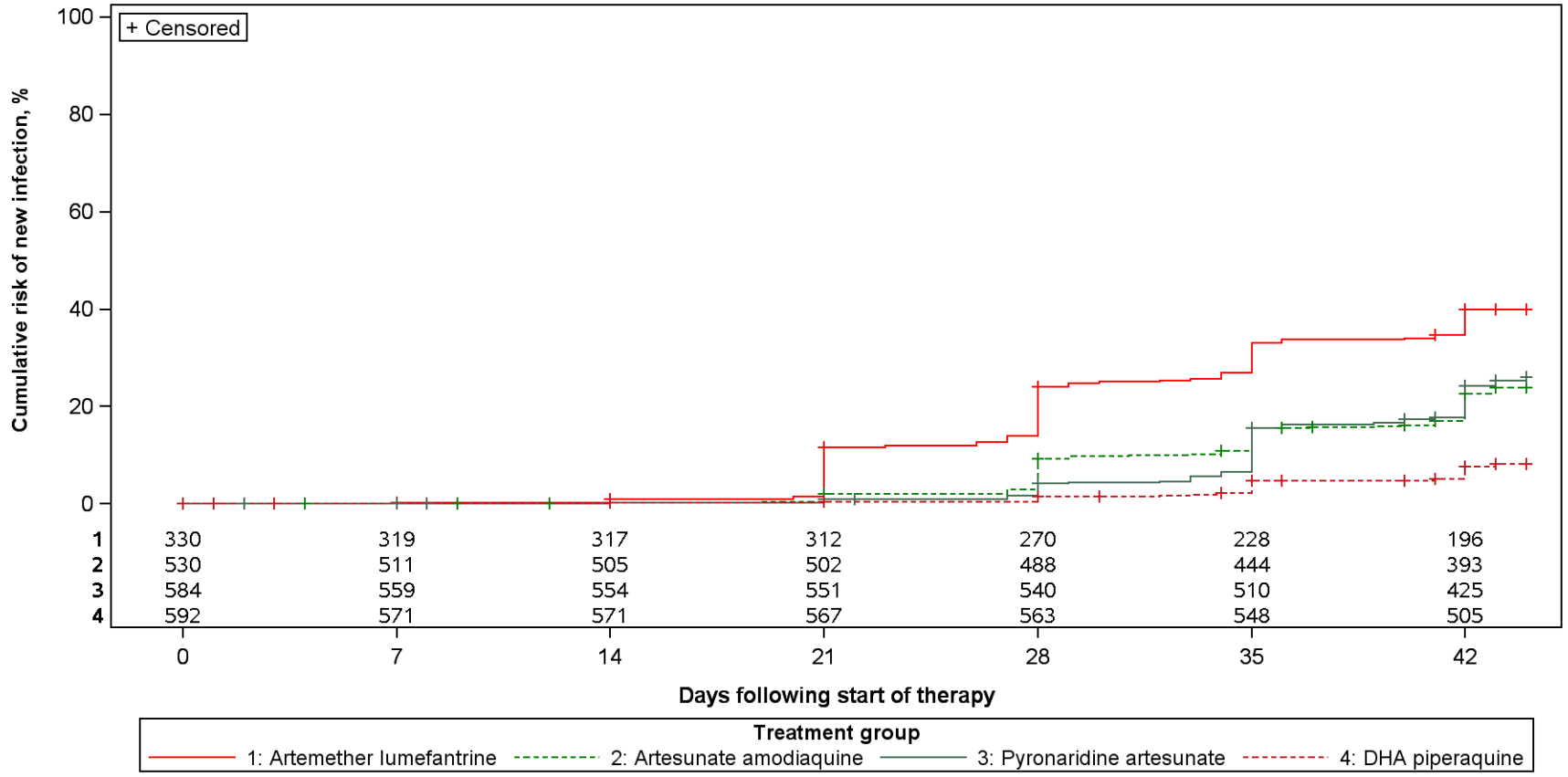

Figure 14.2.2.2 Kaplan-Meier estimates of time until *P. falciparum* recrudescence
Intent-to-treat population

Programming note: Same layout as Figure 14.2.2.1 for recrudescence.

Figure 14.2.2.3 Kaplan-Meier estimates of time until new *P. falciparum* infection
Intent-to-treat population

Programming note: Same layout as Figure 14.2.2.1 for any new infection.

Figure 14.2.2.4 Kaplan-Meier estimates for time until *P. ovale* recurrence
Intent-to-treat population

Programming note: Same layout as Figure 14.2.2.1 for any recurrence of P. ovale.

Figure 14.2.2.5 Kaplan-Meier estimates for time until *P. malariae* recurrence
Intent-to-treat population

Programming note: Same layout as Figure 14.2.2.1 for any recurrence of P: malariae.

Figure 14.2.2.4 Kaplan-Meier estimates of *P. falciparum* parasite clearance time
Intent-to-treat population

Treatment episode 1

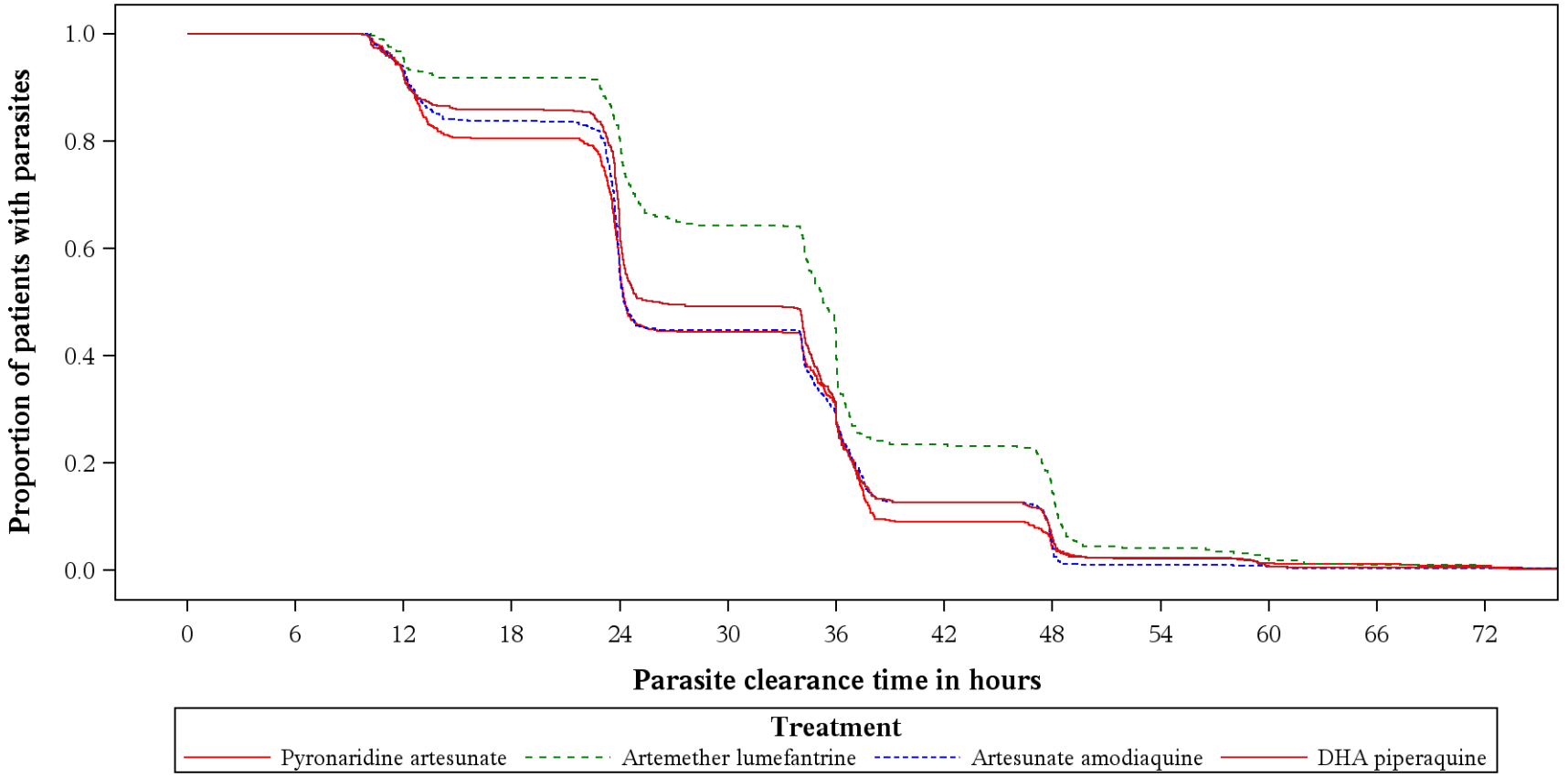

Figure 14.2.2.5 Kaplan-Meier estimates of *P. falciparum* parasite clearance time
Primary Day 28 efficacy evaluable population

Programming note: Same layout as Figure 14.2.2.4

Figure 14.2.2.6 Kaplan-Meier estimates of *P. ovale* parasite clearance time
Intent-to-treat population

Programming note: Same layout as Figure 14.2.2.4

Figure 14.2.2.7 Kaplan-Meier estimates of *P. malariae* parasite clearance time
Intent-to-treat population

Programming note: Same layout as Figure 14.2.2.4

Figure 14.2.3.1 Mean number of P. *falciparum* gametocytes over time
Intent-to-treat population – Patients with no P. *falciparum* gametocytes at Day 0 but with gametocytes thereafter
(Page 1 of 1)

Treatment episode 1

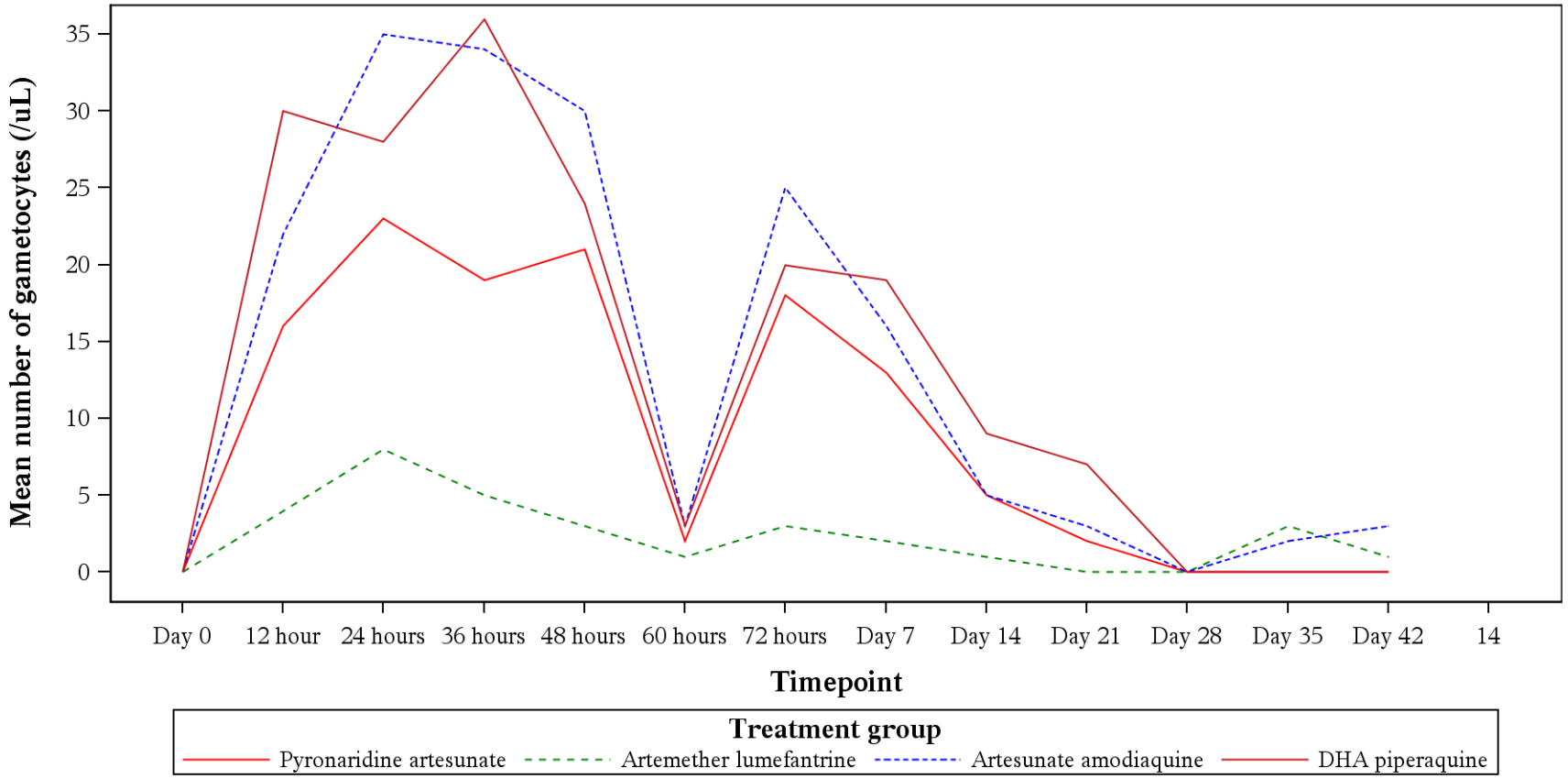

Figure 14.2.3.2 Mean number of *P. falciparum* gametocytes over time
Intent-to-treat population – Patients with *P. falciparum* gametocytes at Day 0

Programming note: Same layout as Figure 14.2.3.1 but for patients who had gametocytes at Day 0.

Figure 14.3.2.1 Scatter plot of peak bilirubin versus peak ALT >= Day 3, by treatment episode
Overall safety population
(Page 1 of 1)

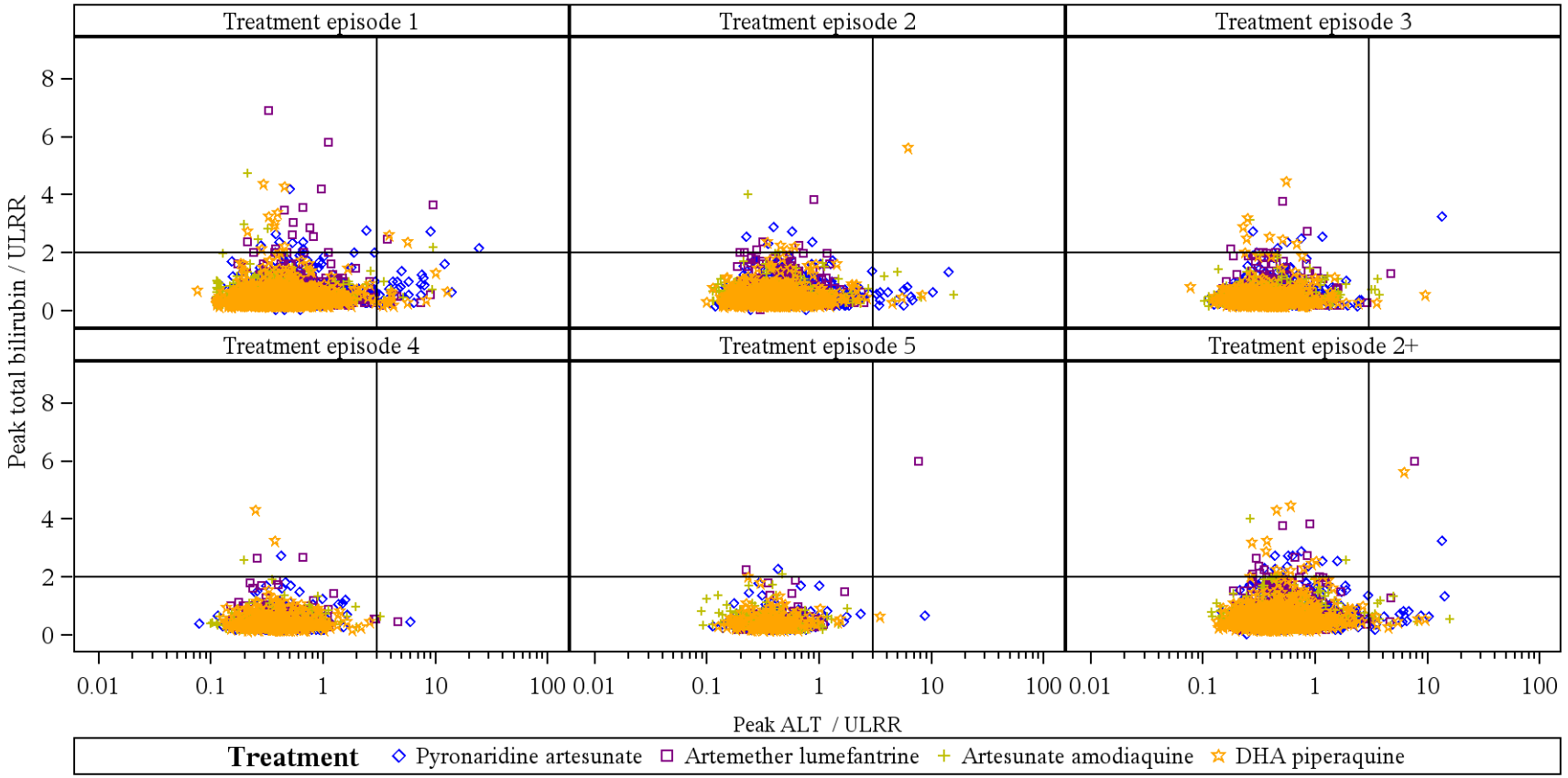

Figure 14.3.2.2 Scatter plot of peak bilirubin versus peak AST >= Day 3, by treatment episode
Overall safety population

Programming note: same layout as Figure 14.3.2.1

Figure 14.3.2.3 Scatter plot of peak bilirubin versus peak ALT >= Day 7, by treatment episode
Overall safety population

Programming note: same layout as Figure 14.3.2.1

Figure 14.3.2.4 Scatter plot of peak bilirubin versus peak AST >= Day 7, by treatment episode
Overall safety population

Programming note: same layout as Figure 14.3.2.1

Figure 14.3.2.5 Scatter plot of ALT over time, by treatment episode
Overall safety population

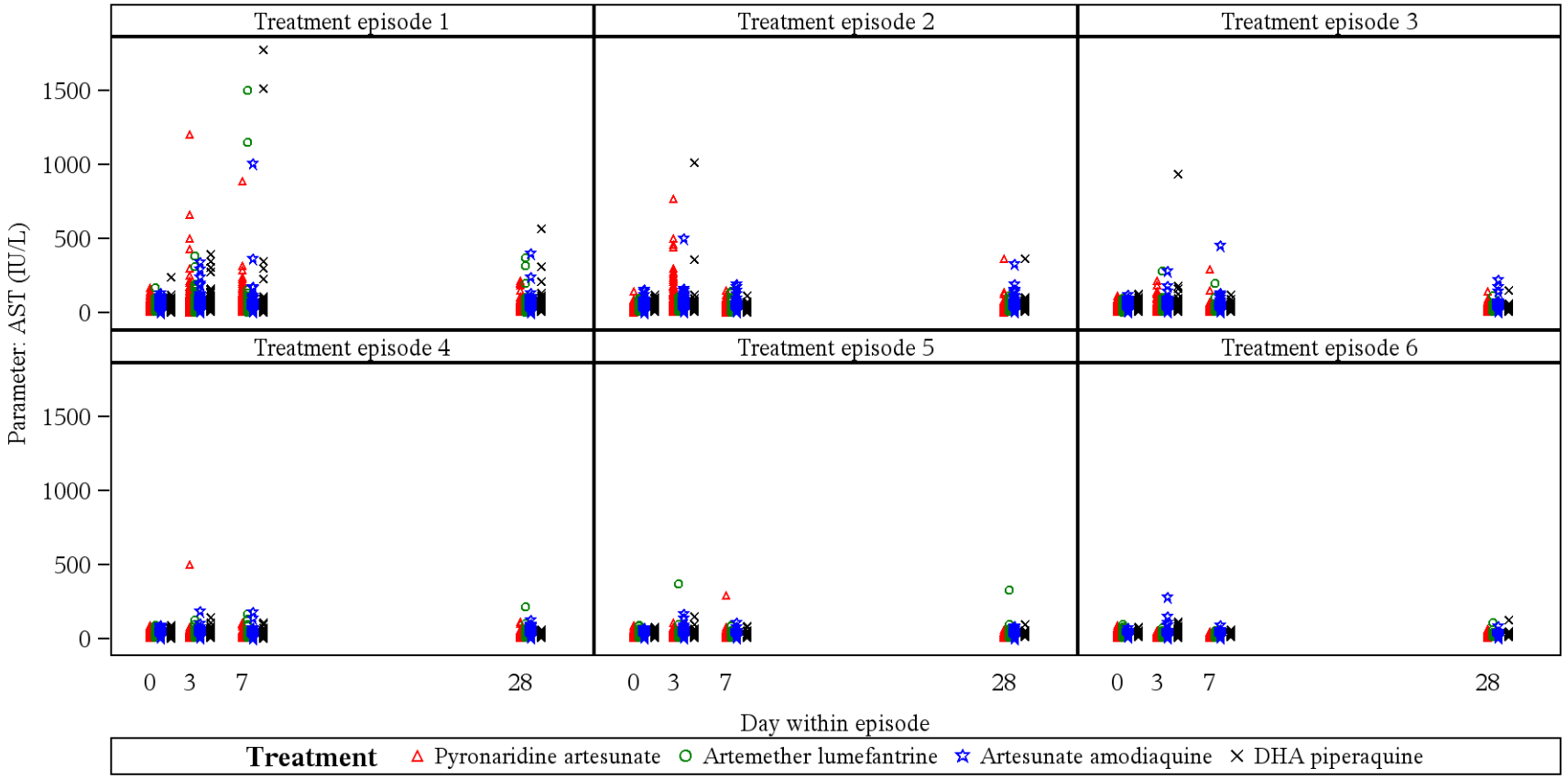

Figure 14.3.2.6 Scatter plot of ALT over time, by treatment episode
Overall safety population

Programming note: same layout as Figure 14.3.2.5

Figure 14.3.2.7 Scatter plot of total bilirubin over time, by treatment episode
Overall safety population

Programming note: same layout as Figure 14.3.2.5

Listing 14.3.1.1 Listing of serious adverse events
Overall safety population
(Page 1 of 1)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No.	Adverse event INVESTIGATOR TERM/ Preferred term/SOC	Start date/ day	Stop day/ day	Severity	Relation-ship with study drug	Action taken	Outcome
xx-xxxx	8/F/xx.x	1	XXXXXXXXXXX/ xxxxxxxxxxxx/xxxxxxxxx	ddMMMyyyy/xx	ddMMMyyyy/xx	mild	possible	none	resolved
		#							
etc.									

Day 0 is defined as the date of first study drug administration within actual treatment episode.
Action taken: 1 = none, 2 = treatment stopped, 3 = remedial treatment, 4 = hospitalization, 5 = other
Episode treated with quinine.

Listing 14.3.1.2 Listing of liver function test values for all patients with an AST or ALT value >3x ULN or a total bilirubin value > 1.5 x ULN event
Overall safety population
(Page 1 of n)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No.	Parameter	Unit	Normal range	Visit	Visit date/ day	Value	Criterion
xx-xxxx	8/F/xx.x	1	AST	U/L	xx.x - xx.x	Day 0	ddMMMyyyy/ 0	xx.x	
						Day 3	ddMMMyyyy/ 3	xx.x	> 5 x ULN #
						Day 7	ddMMMyyyy/ 7	xx.x	
etc.			ALT						
			Total bilirubin						

Day 0 is defined as the date of first study drug administration within actual treatment episode.
# denotes a newly occurring or worsening event compared to Day 0 of actual episode.

Programming note: If a patient has a hepatotoxicity event at any time during the study, list all AST, ALT and total bilirubin values for this patient.

Listing 14.3.1.3 Listing of ECG data for patients with an increase in QTc > 30 msec or a notable QTc value > 500 msec
Overall safety population
(Page 1 of n)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No.	Visit	ECG date/day/time/ hours (1)	Bazett QTc (msec) Value	Bazett QTc (msec) Change from Day 0	Fridericia QTc (msec) Value	Fridericia QTc (msec) Change from Day 0
xx-xxxx	8/F/xx.x	1	Day 0	ddMMMyyyy/xx/hh:mm/xx				
etc.								

(1) since first dose within actual treatment episode
* increase from Day 0 of 30-60 msec; # increase from Day 0 >60 msec; ^ value >500 msec

Programming note: If a patient has a notable QTc at any time during the study, list all QTc values for this patient.

Listing 14.3.1.4 Listing of adverse events for patients < 5 years of age with severe malnutrition
Overall safety population

Programming note: Same layout as Listing 14.3.1.1

Listing 14.3.1.5 Listing of liver function test values for patients < 5 years of age with severe malnutrition
Overall safety population

Programming note: Same layout as Listing 14.3.1.2

Appendix 16.2.1.1 (Page 1 of n)
Listing of study completion (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Total no of episodes*	Completed	Date/day of withdrawal/ completion	Subject summary	Primary reason for withdrawal
xx-xxxx	8/F/xx.x	xxx/xxx		ddMMMyyyy/x	Withdrawn during active treatment period	xxxxxxxxxxxxxxxxxxx
etc.						

* Overall/uncomplicated

Appendix 16.2.1.2 (Page 1 of n)
Listing of protocol deviations or other conditions leading to exclusion from efficacy evaluable analysis (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.		Protocol deviation/ Condition leading to exclusion	Details	Deviation day/day
xx-xxxx	8/F/xx.x	xxx	§#	xxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxx	
etc.						

excluded from all primary efficacy evaluable analyses, § excluded from all secondary efficacy evaluable analyses.
* excluded from certain efficacy evaluable analyses.
Patients who were excluded from primary efficacy evaluable analysis since they were randomised in centres using ASAQ as comparator are not listed here.

Appendix 16.2.1.3 (Page 1 of n)
Inclusion in analysis populations (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Malaria type (current episode)	Safety	ITT	Day 28 EE Crude	Day 28 EE PCR	Day 42 EE Crude	Day 42 EE PCR
xx-xxxx	8/F/xx.x	xxx	P.f.	Yes	Yes	Yes	Yes	Yes	Yes
etc.									

Appendix 16.2.2.1 (Page 1 of n)
Demographic data (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Date of birth	Date of enrolment	Height (cm)	Weight (kg)	Ethnicity group
xx-xxxx	8/F/xx.x	ddMMMyyyy	ddMMMyyyy	xxx	xx.x	xxxxxxxxxxxxx
etc.						

Appendix 16.2.3.1 (Page 1 of n)
Administration of study medication (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Dose No.	Date/time of dosing	Number of tablets/sachets	Patient vomited	Date/time of vomiting
xx-xxxx	8/F/xx.x	1	1	ddMMMyyyy/hh:mm	xx (drug, xxx : xxx mg)	Yes	ddMMMyyyy/hh:mm
			1r	ddMMMyyyy/hh:mm	xx (drug, xxx : xxx mg)	No	
			2	ddMMMyyyy/hh:mm		No	
		2					
etc.							

r = repeat full dosing

Appendix 16.2.3.2 (Page 1 of n)
Use of rescue medication (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Treatment INVESTIGATOR TERM Preferred term	Dose / unit / frequency / route	Date/day started	Date/day stopped/ outcome	Reason for use
xx-xxxx	8/F/xx.x	1	xxxxxxxxxxxxxxx xxxxxxxxxxxxx	xxxxxxxx	ddMMMyyyy/xx	ddMMMyyyy/xx	xxxxxxxxxxxxxxxx
		2					
etc.							

Day 0 is defined as the date of first study drug administration within actual treatment episode.

Appendix 16.2.3.3 (Page 1 of n)
Non study drug treatment episodes (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Treatment INVESTIGATOR TERM/ Preferred term	Dose / unit / frequency / route	Date started	Date stopped/ outcome	Reason for use
xx-xxxx	8/F/xx.x	xxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	ddMMMyyyy	ddMMMyyyy	xxxxxxxxxxxxxxxx
etc.						

Appendix 16.2.3.4 (Page 1 of n)
Concomitant medications (Overall safety population)

Programming note: list patients who received a concomitant medication except rescue medication and non study treatment episodes, same layout as Appendix 16.2.3.2; add footnote "# episode treated with quinine"

Appendix 16.2.4.1 (Page 1 of n)
Derived efficacy variables (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Malaria type	Baseline parasite count(/uL)	Parasite clearance time (h)	Day 28	Day 42	Day 28	Day 42	ETF	LCF Day	LPF Day	[1]	[2]	[3]
xx-xxxx	8/F/xx.x	1 #	P.f.	xxxx	xx.x	yes	yes	no	yes		xx	xx	xx	xx	xx

etc.

Day 0 is defined as the date of first study drug administration within actual treatment episode.
* = time censored
[1] Start day of other medication with antimalarial activity.
[2] Day of withdrawal.
[3] Day of last parasite count within episode.
excluded from all efficacy evaluable analyses.
& excluded from certain efficacy evaluable analyses.

Appendix 16.2.4.2 (Page 1 of n)
Malaria blood smear data (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./ Ana.	Visit	Collection date/ day/time hours (1)	P. *falciparum* AF per 200 WBC	P. *falciparum* AF per µL	P. *falciparum* G	P. *malariae* AF per 200 WBC	P. *malariae* AF per µL	P. *malariae* G	P. *ovale* AF per 200 WBC	P. *ovale* AF per µL	P. *ovale* G
xx-xxxx	8/F/xx.x	1	D 0	ddMMMyyyy/xx/hh:mm/xx.x									
			D 1	ddMMMyyyy/xx/hh:mm/xx.x									
			D 2	ddMMMyyyy/xx/hh:mm/xx.x									
		2											
etc.													
		#											

(1) since first dose within actual treatment episode
AF =asexual forms, G = gametocytes
# episode treated with quinine.

Appendix 16.2.4.3 (Page 1 of n)
Body temperature (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Visit	Date/day/time hours (1)	Body temperature °C	Method
xx-xxxx	8/F/xx.x	1	Day 0	ddMMMyyyy/xx/hh:mm/xx.x	xx.x	Axillary
			Day 1	ddMMMyyyy/xx/hh:mm/xx.x	xx.x	Axillary
			Day 2	ddMMMyyyy/xx/hh:mm/xx.x	xx.x	Axillary
		2				
etc.						

(1) since first dose within actual treatment episode
episode treated with quinine.

Appendix 16.2.5.1 (Page 1 of n)
Adverse events (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	SAE	Adverse event INVESTIGATOR TERM/ Preferred term/SOC	Start date/ day	Stop day/ day	Severity	Relation-ship with study drug	Action taken	Outcome
xx-xxxx	8/F/xx.x	1	No	XXXXXXXXXXX/ xxxxxxxxxxxx/xxxx	ddMMMyyyy/xx	ddMMMyyyy/xx	mild	possible	1	resolved
etc.										

Day 0 is defined as the date of first study drug administration within actual treatment episode.
Action taken: 1 = none, 2 = treatment stopped, 3 = remedial treatment, 4 = hospitalization, 5 = other
episode treated with quinine.

Appendix 16.2.6.1 (Page 1 of n)
Haematology data (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Parameter	Unit	Normal range	Visit	Visit date/ day	Value	
xx-xxxx	8/F/xx.x	1	xxxxxx	xxx	xx.x - xx.x	Day 0	ddMMMyyyy/ 0	xx.x	L
						Day 3	ddMMMyyyy/ 3	xx.x	H
						Day 7	ddMMMyyyy/ 7	xx.x	

etc.

Day 0 is defined as the date of first study drug administration within actual treatment episode.
L = below normal range, H = above normal range
# episode treated with quinine.

Appendix 16.2.6.2 (Page 1 of n)
Biochemistry data (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Parameter	Unit	Normal range	Visit	Visit date/ day	Value	
xx-xxxx	8/F/xx.x	1	xxxxxx	xxx	xx.x - xx.x	Day 0	ddMMMyyyy/ 0	xx.x	L
						Day 3	ddMMMyyyy/ 3	xx.x	H
						Day 7	ddMMMyyyy/ 7	xx.x	
		#							
etc.									

Day 0 is defined as the date of first study drug administration within actual treatment episode.
L = below normal range, H = above normal range
# episode treated with quinine.

Appendix 16.2.7.1 (Page 1 of n)
Vital signs (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Visit	Date/day/time hours (1)	Position	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart rate (bpm)	Respiratory rate (bpm)
xx-xxxx	8/F/xx.x	1	Day x	ddMMMyyyy/xx/hh:mm/xx.x	sitting	xxx	xxx	xxx	xxx
			Day x	ddMMMyyyy/xx/hh:mm/xx.x					
			Day x	ddMMMyyyy/xx/hh:mm/xx.x					
		2							
etc.									
		#							

(1) since first dose within actual treatment episode
episode treated with quinine.

Appendix 16.2.8.1 (Page 1 of n)
ECG results from central reading (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig. /Ana.	Visit	Date/day/time hours (1)	Position	Heart rate (bpm)	PR-interval (ms)	QRS-interval (ms)	RR-interval (ms)	QT-interval (ms)	QTc-interval Bazett (ms)	QTc-interval Fridericia (ms)
xx-xxx	8/F/xx	1	Day x	ddMMMyyyy/xx/hh:mm/xx.x	sitting	xx	xx	xx	xx	xx	xx	xx
			Day x	ddMMMyyyy/xx/hh:mm/xx.x								
			Day x	ddMMMyyyy/xx/hh:mm/xx.x								
		2										
etc.												

(1) since first dose within actual treatment episode
episode treated with quinine.

Appendix 16.2.8.2 (Page 1 of n)
ECG results – abnormalities as recorded at the site (Overall safety population)

Treatment group: Pyronaridine-artesunate

Pat. No.	Age/ Sex/ Weight	Episode No. Orig./Ana.	Visit	Date/day/time/hours (1)	Position	Clinically significant abnormalities	Abnormality details
xx-xxxx	8/F/xx	1	Day x	ddMMMyyyy/xx/hh:mm/xx.x	sitting	yes	xxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx
			Day x	ddMMMyyyy/xx/hh:mm/xx.x			
			Day x	ddMMMyyyy/xx/hh:mm/xx.x			
		2					
etc.							

(1) since first dose within actual treatment episode
episode treated with quinine.