STATISTICAL ANALYSIS PLAN AMENDMENT 1

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

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1. Rationale for amendment

The purpose of this amendment to the analysis plan is to clarify the denominator derivation for the primary efficacy endpoint, in particular adjustments to account for any anti-malarial treatment given during the two-year period, in accordance with the clinical study protocol. In addition the amendment clarifies the statistical analysis model for the primary efficacy analysis with regard to the inclusion of the patient's age as explanatory variable. Finally, two sensitivity analyses of the primary efficacy endpoint are being added to further evaluate the effect of new infections occurring before Day 28 and the use of the whole observation period as denominator.

2. Changes to the statistical analysis plan

2.1 Changes to Section 8.1 – Primary efficacy variable

Change #1

Old text

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

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.

New text

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 and at risk. To estimate the period at risk, the duration of time the patient was observed in the study will be reduced by the time a patient was not at risk to experience malaria, i.e.;

- 27 days following each ACT treatment
- 14 days following each rescue treatment (quinine oral, IM or IV; artesunate IM or IV)
- 14 days for episodes treated completely with quinine or artesunate.

The observation period for the two years will start on Day 28 after the first malaria treatment start within the study. Any patient who was not observed at least 28 days within this study will not be included in this analysis. In case a patient has re-appearance of parasites before Day 28 the exposure time will be reduced by the number of days when the re-appearance occurred, e.g., if there is a re-appearance on Day 22, the exposure time will be reduced by 22 days rather than 27 for this episode. Also, if a patient is not observed for 28 days for the last episode before discontinuing from the study the total time will be reduced only by the number of days the patient was observed for this episode.

Change #2

Old text

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.

New text

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. Age categories (<5, 5-<15,>=15) and treatment by age category interaction will be included in the model. The following code:

PROC GENMOD data = <datafile name>;

class treatment agecat/param=glm ;

model nepi = treatment agecat agecat*treatment /dist=poisson offset=ldur dscale link=log;

run;

where nepi is the number of repeat malaria episodes, treatment is the treatment group and agecat is the age category, 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.

Change #3

The following secondary analyses of the primary efficacy endpoint will be added:

- Using the full two year observation period in the denominator.
- Adding any new infection (confirmed by PCR) before Day 28 as an additional episode to the numerator and using: i) the treatment adjusted exposure time as the denominator and ii) full two year observation period in the denominator .

All incidence rates will be calculated as
# of repeat episodes / exposure time * 730 to get a standardized estimate for the two years.