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STEFFEN WITTE (1), PETER MEISSNER (2), ANJA SCHULDT (1) , ULRICH MANSMANN (1,3)

(1) Institut für Medizinische Biometrie und Informatik (IMBI), Universität of Heidelberg,
(2) Department of Tropical Hygiene and Public Health, University of Heidelberg, Germany
(3) Institut für Med. Informationsverarbeitung, Biometrie und Epidemiologie, LMU München

with coworkers

GERMAIN MANDI (3), THÉOPHILE TAPSOBA (3), OLAF MÜLLER (2), THOMAS JUNGHANSS (2), BOUBACAR COULIBALY (3), JENS RENGELSHAUSEN (4), WOLFGANG SCHIEK (5), ALBRECHT JAHN (2), MAMADOU SANON (3), INGEBORG WALTER-SACK (4), GERD MIKUS (4), JÜRGEN BURHENNE (4), KLAUS-DIETER RIEDEL (4), HEINER SCHIRMER (6), BOCAR KOUYATÉ (3)

(3) Nouna Health Research Centre (CRSN), Nouna, Burkina Faso; (4) Department of Internal Medicine VI, Clinical Pharmacology and Pharmacoepidemiology, Ruprecht-Karls-University, Heidelberg, Germany; (5) DSM Fine Chemicals, Linz, Austria; (6) Biochemie-Zentrum, Ruprecht-Karls-University, Heidelberg,Germany

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3 Abbreviations

ACPR	adequate clinical and parasitological response
CHI	Chi-square (continuity corrected)
CI	confidence interval
CQ	chloroquine
ETF	early treatment failure
FAS	full analysis set (an analysis population)
Hb	haemoglobin
Hct	haematocrit
LCF	late clinical failure
LPF	late parasitological failure
ITT	intention to treat
MB	methylene blue
PCR	polymerase chain reaction
PP	per protocol (an analysis population)
SAF	safety population (an analysis population)
SOC	system organ class (MedDRA coding)
TF	treatment failure (ETF or LCF)
WMW	Wilcoxon Mann Whitney (U-Test)

4 Summary

Background: Safe, effective and affordable drug combinations against falciparum malaria are urgently needed for the poor populations in malaria endemic countries. Chloroquine (CQ) combined with methylene blue (MB) is one promising new regimen.

Objectives: The primary objective of this study was to evaluate the safety of CQ-MB in African children with uncomplicated malaria. The secondary objectives were to assess the efficacy and the acceptance of MB in a rural population of western Africa.

Methods: In this hospital-based randomized controlled trial (ISRCTN27290841), 226 children (6-59 months) with uncomplicated falciparum malaria were treated in Burkina Faso. The children were 4:1 randomized to CQ-MB (n=181; 25mg/kg CQ and 12mg/kg MB over three days) or CQ (n=45; 25mg/kg over three days) respectively. Primary outcome was the incidence of severe haemolysis or other serious adverse events (SAEs). Patients were hospitalised for 4 days and followed-up until day 14.

Results: No differences in the incidence of SAEs and other adverse events were observed in G6PD sufficient (n=157) and G6PD deficient (n=24) children treated with CQ-MB. There was no case of severe haemolysis and also no significant difference in mean haemoglobin between study groups. Treatment failure rates were 53.7% (95% CI [37.4%; 69.3%]) in the CQ group compared to 44.0% (95% CI [36.3%; 51.9%]) in the CQ-MB group.

Conclusion: CQ resistance has reached unacceptable high levels in urban Burkina Faso. CQ-MB is safe for the treatment of uncomplicated malaria, even in G6PD deficient African children. However, the efficacy of this combination has not been sufficient at the MB dose used in this study. A dose-finding study is under way which will determine the efficacy of this combination at higher doses of MB.

5 Introduction

Malaria is responsible for 1.5 – 2.7 million deaths per year and represents one of the five major disease burdens responsible for the mortality in children less than five years especially in African countries (WHO 1997, Breman et al. 2004). Only a few safe and effective chemotherapeutic agents are presently affordable for most sub-Saharan African (SSA) populations (Bloland et al. 2000; Winstanley 2001). The increasing resistance of *Plasmodium falciparum* to chloroquine and other antimalarials like sulphadoxine/ pyrimethamine supports

the urgent need for development of new drugs against malaria (Trapé 2001). The combination of the drugs chloroquine (CQ) and methylene blue (MB) is a promising new regimen (Schirmer 2003).

MB was already successfully used over 100 years ago for the treatment of malaria, even in children (Guttmann and Ehrlich 1891; Ehrlich 1913; Ferreira 1893). It was forgotten as other drugs (e.g. chloroquine) were introduced on the market. MB is a registered drug for the treatment of methemoglobinemia and in cancer treatment at i.v. dosages of 1-2 mg/kg (Küpfer et al. 1994). In recent years *in vitro* experiments have confirmed the antimalarial potency of MB (Amaral et al. 2001). MB has been shown to specifically inhibit the glutathione reductase of the malarial parasite (Sarma et al. 2003). Furthermore it has the potential to reverse grade I/II CQ resistance (Färber et al. 1998; Meierjohan et al. 2002).

There is some concern, that the application of MB could be followed by haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals in malaria-endemic regions. In erythrocytes the main role of G6PD is to produce antioxidant potential in the form of reduced nicotinamide adenine dinucleotide phosphate (NADPH) to protect cells against oxidative damage. In most of Westafrica, the milder form (class III) of G6PD deficiency dominates (Fleming and Silva 2003). However there is evidence for the risk for haemolysis in G6PD deficiency not depending on the dose level (Beutler 1994, Vulliamy and Luzzatto 2003).

Against this background, two studies on the safety of the combination CQ-MB have been implemented in adult populations in 2003. The combination regimen was well tolerated in healthy G6PD sufficient adult males and females from Germany and in healthy G6PD deficient adult men from Burkina Faso (Rengelshausen et al. 2004; Mandi et al. 2005). The primary objective of the present trial was to study the safety of CQ-MB in young African children with uncomplicated falciparum malaria.

6 Material and Methods

6.1 Study area and study subjects

The study was conducted in October and November 2003 in the District Hospital of Nouna in the province of Kossi in north-western Burkina Faso. The town has about 20000 inhabitants of different ethnic groups. Most people living in nearby villages are farmers. Formal health services in this province are restricted to the district hospital and to 22 small health centres. Access to health services is limited, particularly during the rainy season (Müller et al. 2003a).

The area is highly endemic for P. falciparum malaria (Müller et al. 2001). CQ is currently still the first-line treatment in Burkina Faso. Day 14 CQ clinical failure rates in the villages surrounding Nouna town were shown to be around 10% in recent years (Müller et al. 2003b). The overall prevalence of G6PD deficiency in the Nouna study area has been shown to be 14% (Schirmer et al. 2003).

Children aged 6-59 months with uncomplicated falciparum malaria (axillary temperature ≥ 37.5°C and ≥ 2.000 P. falciparum asexual parasites per µl blood) whose parents or caretaker had given informed consent were enrolled into the study. Most children were from the Town of Nouna, some few children were from villages close to Nouna. Children with complicated or severe malaria (repeated vomiting, seizures or other neurological impairment), anaemia (haemoglobin < 8 g/dl or haematocrit < 24%) or any other apparent significant disease (e. g. pneumonia, meningitis, hepatitis, severe diarrhoea, measles, severe malnutrition) were excluded from the trial.

6.2 Study objectives

The purpose of the study was to gain first information on the safety and efficacy profile of an affordable new drug combination for the treatment of uncomplicated falciparum malaria in African children. The *primary objective* of this study was to determine and compare serious adverse events of CQ-MB and CQ in the treatment of young children with uncomplicated falciparum malaria in western Africa.

Justification: Both CQ and MB are known to be safe in children for other indications. But the combination of CQ and MB has never been used against malaria in children. Therefore we had to investigate all possible SAEs, and in particular haemolysis in G6PD deficiency. Episodes of haemolysis and jaundice in case of significant G6PD enzyme deficiency was caused by an exposure to various drugs and chemicals. As methylene blue belongs to the group of drugs which can probably cause these side effects in G6PD deficient persons and as G6PD deficiency is frequent in Africa, it is of overriding importance to exclude a public health relevant occurrence of such side effects for a candidate malaria drug.

The secondary objectives of this study were:

- to compare the efficacy of CQ-MB and CQ in the treatment of young children with uncomplicated falciparum malaria in western Africa
- to compare the safety of CQ-MB and CQ in the treatment of young children with uncomplicated falciparum malaria in western Africa

- to study the pharmacokinetics of the combination of CQ-MB in children with uncomplicated falciparum malaria in western Africa (published elsewhere)
- to assess the acceptance of methylene blue in a rural population of western Africa

Justification: Efficacy parameters were analysed to gain first information on this new drug combination and to provide details for planning of a consecutive phase III trial. Both CQ and MB are known to be safe in children for other indications. But the combination of CQ and MB has never been used against malaria in children. Therefore serious (primary), non-serious (secondary) and further safety aspects will be investigated. Phase I and I/II studies provided only pharmacokinetic data from European and African adults respectively. This trial will give information on pharmacokinetic data from African children with malaria (published elsewhere). It is known that MB colours the urine and consequently the clothes of children's mothers. Therefore, it is important to investigate the cultural acceptance of this unavoidable side effect.

Post hoc objectives (not stated in the study protocol):

- to compare in vivo resistance rates to CQ and CQ-MB of Nouna town and the surrounding villages
- to compare the prevalence of the main CQ-resistance marker pfcrt K76T between urban and rural areas
- to study the association between the prevalence of the mutation *pfcrt* T76 and total clinical failures

Justification: Resistance to CQ has reached high levels in recent years. Little is known about variation of drug resistance between urban and rural areas.

6.3 Primary endpoints

- Incidence of acute life-threatening haemolysis in G6PD deficient children (definition: haemoglobin ≤ 5 g/dl and haematocrit ≤ 15%, or received blood transfusion according to clinical judgement of study physician) during treatment until 24 hours of last drug application.
- Incidence of serious adverse events in children

6.4 Secondary endpoints

- Incidence of early treatment failures (ETF): development of danger signs or severe malaria on D1-D3 in the presence of parasitaemia OR parasitaemia on D2 higher than D0 count irrespective of axillary temperature OR parasitaemia on D3 with axillary temperatrure ≥ 37.5°C OR parasitaemia on D3 ≥ 25% of count on D0.
- Incidence of late clinical failures (LCF): development of danger sings or severe malaria after D3 in the presence of parasitaemia, without previously meeting any of the criteria of ETF OR presence of parasitaemia and axillary temperature ≥ 37.5°C on any day from D4 to D14, without previously meeting any of the criteria of ETF. Additional to the WHO-Definition: Patients who received quinine and/or sulfadoxine/pyrimethamine on any day from D4 to D14 were considered as LCF.
- Incidence of late parasitological failures (LPF): presence of any parasitaemia on D14 and axillary temperature < 37.5°C, without previously meeting any of the criteria of ETF or LCF.
- Incidence of treatment failures (TF): ETF or LCF.
- Explorative analysis was done regarding ETF, LCF, TF, LPF for subgroups: children younger than 2 years and other, children from Nouna town or from the villages.
- Fever clearance time (definition: time from begin of treatment to the last measurement of an axillary temperature ≥ 37.5°C)
- Parasite clearance time (definition: time from begin of treatment to the last occurrence of detectable parasitaemia)
- Changes in: haemoglobin (D2 – Baseline), haematocrit (last value of D3 – Baseline, D14 – Baseline), creatinine (D2 – Baseline)
- Relation between Hb and Hct (correlation and prediction of Hb)
- Incidence of observed and self-reported non-serious adverse events over the 14 days observation period (MedDRA coding was used)
- Monitoring of concomitant drug intake
- Acceptance of the CQ+MB treatment compared to CQ measured by a standardised questionnaire on day 14 with mothers/caretakers (free text was categorized to 0=no problem 1=slight problems, but acceptance does not influence the drug intake, 2=problems running against the drug intake)

- Sensitivity and Specificity of the modified Beutler-Mitchell-Test for the G6PD status (using a PCR method as the gold standard)
- prevalence of the mutation *pfcrt* K76T (genetic resistance to CQ) and its impact on TF
- Whole blood chloroquine and methylene blue population kinetics (published elsewhere)

Justification: Clinical and parasitological failure rates as well as fever and parasite clearance times are standard endpoints to judge the efficacy of malaria drugs. The blood parameters will be used to investigate potential toxicity of the study drugs. Concomitant drugs may interfere with safety and efficacy endpoints.

Definitions: D0 starts with the first drug intake in the trial for each individual. 24 hours later D1 starts. D14 was defined as a small period of time: -2/+3 days, therefore D14 = (288h, 432h]. When there are two parasite counts or lab values given: the latest was used. For the fever measurement on one day the maximum per day was used. If a patient had no parasitological data on D2 but on D3 this was not considered as failure just due to missing data.

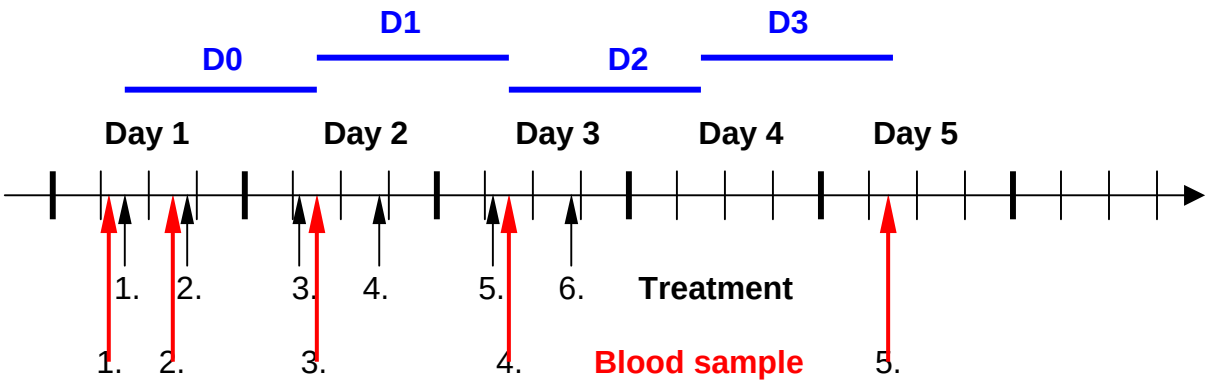

Figure 6-1: Treatment and blood sample for the first five days

6.5 Study design

The study was designed as a sex-stratified (males : females, 4 : 1) parallel group randomised controlled trial (RCT). In each sex stratum, children were block randomised by envelopes to receive either treatment with CQ or CQ-MB by computer-generated randomly permutated codes. Randomisation ratio of CQ-MB : CQ was 4 : 1. The unbalanced stratification and randomisation scheme was justified by the need to achieve a high number of G6PD deficiency children treated with CQ-MB. The prevalence of G6PD deficiency in boys under 5 is 18% while the prevalence in girls is below 4% (Coulibaly et al. 2005). The study was open

label, with blinding only for the laboratory technicians responsible for parasite determination in blood smears.

6.6 Laboratory work-up

At inclusion, every day in hospital, and at day 14 a blood sample for malaria diagnosis (thin and thick blood smears) were measured. The microscopic results (Giemsa-staining) were cross checked by two experienced persons. Thick and thin blood films were analysed for the species-specific asexual parasite density per µl by counting against 200 white blood cells and multiplying by 50. Slides were declared negative if no parasites were seen in 400 fields on the thick film. Furthermore, haemoglobin and haematocrit values as well as plasma serum creatinine levels were monitored.

The G6PD status was determined at inclusion using the NADPH fluorescence test of Beutler and Mitchell (1968) in miniaturized form (Coulibaly 2004, Coulibaly et al. 2005). In short, (20 to) 50 µl blood was collected in a 0.65 ml Eppendorf cap containing (1 to) 2 µl 70 mM EDTA. After mixing the sample, it was stored at 4 °C (where it is stable for 3 weeks). Before the actual test, the sample was diluted with phosphate-buffered saline to give 4g Hb/dl. This standardization is necessary because of the prevalence of anaemia in malaria-endemic regions. 10 µl sample was added to 100 µl screening mixture, and a 20 µl spot of this mixture was placed on filter paper. From the rest of the mixture after 5 to 10 minutes, respectively, two further spots were applied. In G6PD sufficient samples, the first spot was slightly and the second and third spot were brightly fluorescent under the uv-lamp. G6PD deficient samples showed little or no fluorescence in either spot. Control samples were always examined together with the unknown patient samples. The G6PD result was later validated by PCR at the Tropical Institute in Berlin (Germany). Sequences flanking the potential mutations were amplified in two separate nested PCR assays according to Kotea et al. (1999). The alleles were distinguished by restriction fragment length polymorphism. Genetic resistance to CQ was estimated by analyzing the prevalence of the mutation *pfcrt* K76T according to Djimdé et al. (2001).

The G6PD status was determined at the laboratory of the Centre de Recherche en Santé de Nouna (CRSN), using the NADPH fluorescence test of Beutler and Mitchell (1968) in miniaturized form (Coulibaly et al. 2005). 20-50 µl blood was collected in an Eppendorf cap containing 1-2 µl 70 mM EDTA. The sample was stored at 4 °C (it is stable for 3 weeks), and diluted before testing with phosphate-buffered saline to 4g Hb/dl. This standardization is necessary to account for the high prevalence of anaemia. A 10 µl sample was mixed with 100 µl screening solution, and a 20 µl spot dropped on filter paper. Two additional spots were

prepared from the mixture after 5 to 10 minutes. In G6PD normal subjects, the first spot was slightly and the additional spots were brightly UV-fluorescent. G6PD deficient samples showed little or no fluorescence in either spot. Control samples were run in parallel.

6.7 Sample size justification

The trial was designed to show that the risk of haemolysis in the CQ-MB treatment group for children with G6PD deficiency does not exceed 20%. With the alternative of a 2% risk the sample size of 22 children with G6PD deficiency in the CQ-MB treatment group was needed to perform a test on level α=0.05 with a power of 0.9.

To reach the sample size needed for the G6PD subgroup in the CQ-MB treatment group a total of 180 patients was planned (considering a drop-out rate of 6% results in 169 patients). Due to the fact that 20% of males but only 5% of females are G6PD-deficient we chose a 4:1 sex-stratification (males: 135, females: 34). Based on a binomial distribution the number of 22 male G6PD subjects treated with CQ+MB were recruited with a probability of 93% within the first 169 patients. In case of not reaching the number of 22 male G6PD subjects treated with CQ+MB the trial would have been extended until the number of 22 is reached. Therefore a 4:1 allocation to the treatment groups was chosen. This implied a total sample size of 180+45=225 children.

From a public-health related risk benefit calculation it follows that a risk for life-threatening haemolysis above 10% is not acceptable for a first-line anti malaria drug. A less effective anti-malaria treatment forces to reduce the upper limit of life-threatening haemolysis below 10% to counterbalance the malaria and haemolysis induced death in the population.

The argument for the risk benefit calculation was the following:

- Roughly 20% childhood mortality in malaria endemic areas of sub-Saharan Africa, of which 1/4 (5%) is directly caused by malaria
- Thus at least 1% mortality is directly caused by malaria per year in children under the age of five years in malaria endemic areas of sub-Saharan Africa
- A G6PD deficiency prevalence of at least 10% in the CRSN study area
- Every child in the CRSN study area will be treated at least once per year with the existing first-line malaria drug (e.g. CQ-MB)

- The anti-malaria drug eliminates malaria related mortality but implies life-threatening haemolysis in the group of G6PD deficient children. The mortality in the population will be below 1% (< 0.1*0.1)

In this Phase II study it was clear that we were not able to reach the appropriate sample size in the G6PD deficient subpopulation to prove a risk of life-threatening haemolysis below 10%. The recruitment of a G6PD deficient subgroup of appropriate sample size would imply a genetic screening of the children population which is ethically questionable.

Therefore, the following strategy was applied: In order to exclude an unacceptable high risk of life-threatening haemolysis, this study was designed to exclude a risk above 20%. If the study could assess a risk below 20%, the following Phase III study will afford enough information to judge the appropriate risk profile (<10%) for life-threatening haemolysis in the G6PD deficient subgroup.

6.8 Statistics

Primary: The significance level (type I error) for all analysis is set to 0.05. The two primary endpoints will be hierarchically tested. Therefore, no adjustments for multiple tests are necessary. The analysis will be done for the FAS. The PP set is used as sensitivity analysis.

For the first primary endpoint "Incidence of acute life-threatening haemolysis in G6PD deficient children during treatment until 24 hours of last drug application" the following hypothesis will be tested, where p is the probability for haemolysis during 24 hours follow-up after last drug application: H_0: $p \geq 0.2$ versus. H_1: $p < 0.2$ An exact 95% one-sided confidence interval will be given.

For the second primary endpoint "Incidence of serious adverse events" the following hypothesis will be tested $\delta = 1$, where λ_{CQ} is the incidence in the CQ treatment group, λ_{CQ+MB} is the incidence in the CQ+MB treatment group, and $\delta = \lambda_{CQ+MB} / \lambda_{CQ}$ the corresponding relative risk. Chi-square test for differences of incidence of SAEs, 95% CI for the relative risk of SAE rates in treatment groups.

Secondary: All analyses for the secondary analyses have explorative character. 95% Confidence intervals, Wilcoxon-Mann-Whitney-Tests (U-Test, WMW), continuity corrected Chi-Square-Tests (Chi) and/or descriptive statistics were used. Analysis regarding the genetic resistance: The treatment failures were modelled using three binary variables: treatment group (CQ, CQ-MB), genetic resistance (K76T=pfcrt resistant, 76T not resistant), and regional

provenance (Nouna town, rural area). A backward selection was used to eliminate interaction and/or effects using a p-value of 0.2 as a cutoff.

Missing Values: In case of missing information for binary primary or secondary endpoints, the corresponding value was set to failure. For the secondary endpoints fever and parasite clearance time, techniques for censored observations was used. No imputation process was applied.

Software: All evaluations were carried out using the software package SAS® System 8.2 (SAS Inc., Cary/NC, USA).

6.9 Defintions of analysis populations

Two analysis sets were defined: the Safety Set (SAF) and Full Analysis Set (FAS) were identical in this trial and the Per-Protocol Set (PP). FAS was used in general but especially the efficacy parameter were analyzed with the PP set as well. The FAS is more conservative in this context but for a realistic estimation and a proof of principle the PP is more appropriate.

- Safety Set (SAF) = Full Analysis Set (FAS): This analysis set will consist of all patients who received active trial medication at least once (not based on pharmacokinetic confirmation). Patients are analysed as randomised.
- Per-Protocol (PP) Set: This analysis set will consist of all patients included in the full analysis set and treated on D0-D2: once for patients in the CQ group and twice for patients in the CQ+MB group. The following patients will be excluded:
    - Patients who vomited and the drug was not given again
    - Patients who vomited and it is unclear whether it was given again
    - Patients who violate inclusion/exclusion criteria
    - Patients assigned to the combination group (CQ+MB) without blue urine
    - Patients received quinine and/or sulfadoxine/pyrimethamine and being LCF due to the extension of the WHO definition of LCF (chapter 6.4)

6.10 Interventions

All study children received a standard total dose of 25mg/kg of CQ syrup (10mg/ml) over a period of three days (first and second day: 10mg/kg, third day: 5mg/kg). Chloroquine was taken from the essential drug stock of the Ministry of Health. The CQ-MB group additionally

received orally a 0.5% MB solution (4 mg/kg/day) for three days, divided into morning and evening doses (produced by Mayrhofer Pharmazeutika / Linz, Austria).

All study children were hospitalised for four days, and administration of study medications was directly supervised by a study physician or a study nurse. At least once during the time of hospitalisation the colour of the urine was checked to assess MB compliance through visual observation. In case of vomiting within half an hour after the study medication, the medication was repeated. All drugs were allowed as concomitant treatments, except dapsone and other sulfones, acetanilide and phenacetin, nalidixic acid, niridazole, nitrofurantoins and sulphonamides (themselves known to cause haemolysis in G6PD deficiency) (Fleming and Silva 2003). All children having fever ≥ 38.5°C received standard doses of paracetamol (10 mg/kg) until symptoms subsided.

Study subjects and caretakers were questioned for adverse effects and examined for signs of haemolysis by the study physicians twice daily until discharge from hospital and after 14 days. Acceptance of MB was evaluated at day 14.

6.11 Ethical, organizational and regulatory aspects

The trial was conducted in accordance with local laws and the internationally established principles for Good Clinical Practice (including statistical monitoring and site monitoring) which had their origin in the Declaration of Helsinki of the World Medical Association and in accordance with the "Note for Guidance on Clinical Investigation of Medicinal Products in Children". The study protocol was approved by the ethics committees in Heidelberg and Burkina Faso. A scientific advisory board was established and it gave advice during the planning phase. The safety of the trial was also monitored by a data safety monitoring board (DSMB). An analysis plan was written before data bank closure.

After having received detailed information from the study physician about all risks and benefits of the study through translation of a detailed research consent form into the local language, caretakers were asked for their written consent. They were clearly informed that they could withdraw from the study at any time and without disadvantage. A standard blood transfusion service was available at the hospital and study physicians and emergency medications were available 24 hours per day. All children in the specified age group who were presented to the hospital during the study period for other conditions besides malaria also received free treatment.

7 Results

The main results are already published (Meissner et al. 2005). This report gives the same results plus some additional information which can not be published in a short journal paper.

7.1 Recruitment of patients

The first patient was screened on the 13th of October 2003, the last on the 23rd of November 2003. 229 children with uncomplicated malaria were enrolled (Figure 7-1, Table 12-1).

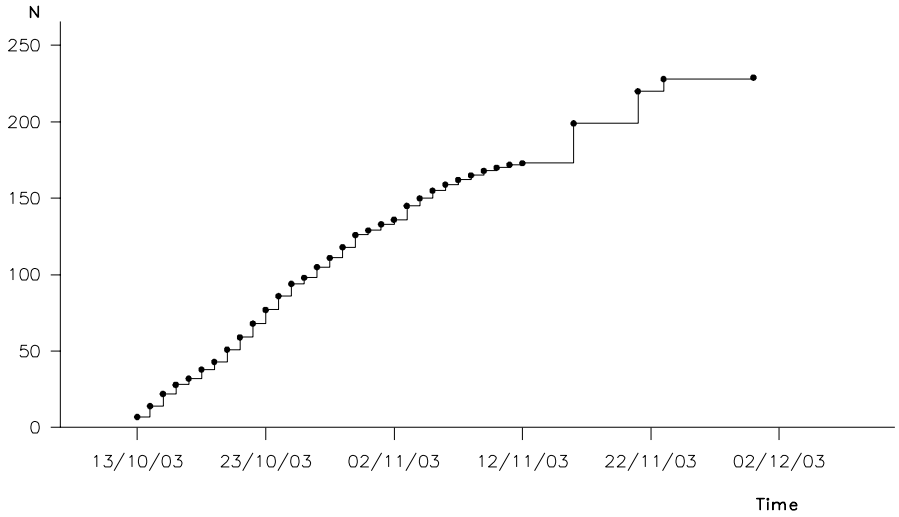

Figure 7-1: Recruitment of patients

7.2 Analysis Sets and Compliance

Three boys in group CQ-MB were excluded on day one. One boy left for family reasons before application of the first medication, two refused to take the first dose of MB (Figure 7-2). The following analysis is based on the remaining 226 children. This is the a priori defined full analysis set (FAS) for the intention to treat analysis, 45 receiving CQ and 181 CQ-MB. The PP set consists of 207 children. In the CQ group only 4 patients were not treated per protocol. Fifteen patients in the CQ-MB group were not per protocol due to treatment (1), vomiting (5), violation of eligibility criteria (1), lost to follow-up (4), and a treatment of antimalarials between day 5 and day 14 without fever, see Table 12-2.

Using strictly the WHO definition 6 children (Nr. 135, 140; 102, 103, 166, 276) would be ACPR (adequate clinical and parasitological response = not ETF, LCF, or LPF) but they received quinine and/or sulfadoxine/pyrimethamine between day 5 and day 14. They are

therefore considered as LCF in the ITT-analysis of the full analysis set (FAS) and considered as protocol violator (not in the PP set).

Figure 11-1 and Figure 11-2 visualize the baseline blood sample and treatment applications for each individual patient. Only 2+1=3 patients did not follow the drug application schedule (Table 12-2, Table 12-40). All children in the CQ-MB group had at least once a blue urine, and non of the patients in the CQ group.

The time from baseline blood measurement to first treatment was quite long: the average and standard deviation of 7.8 +/– 2.3h (CQ) and 7.4 +/– 2.5h (CQ-MB) with a total range of 2.7 to 13.8h. This has to be improved in further trials (Table 12-8, Figure 11-1, Figure 11-2).

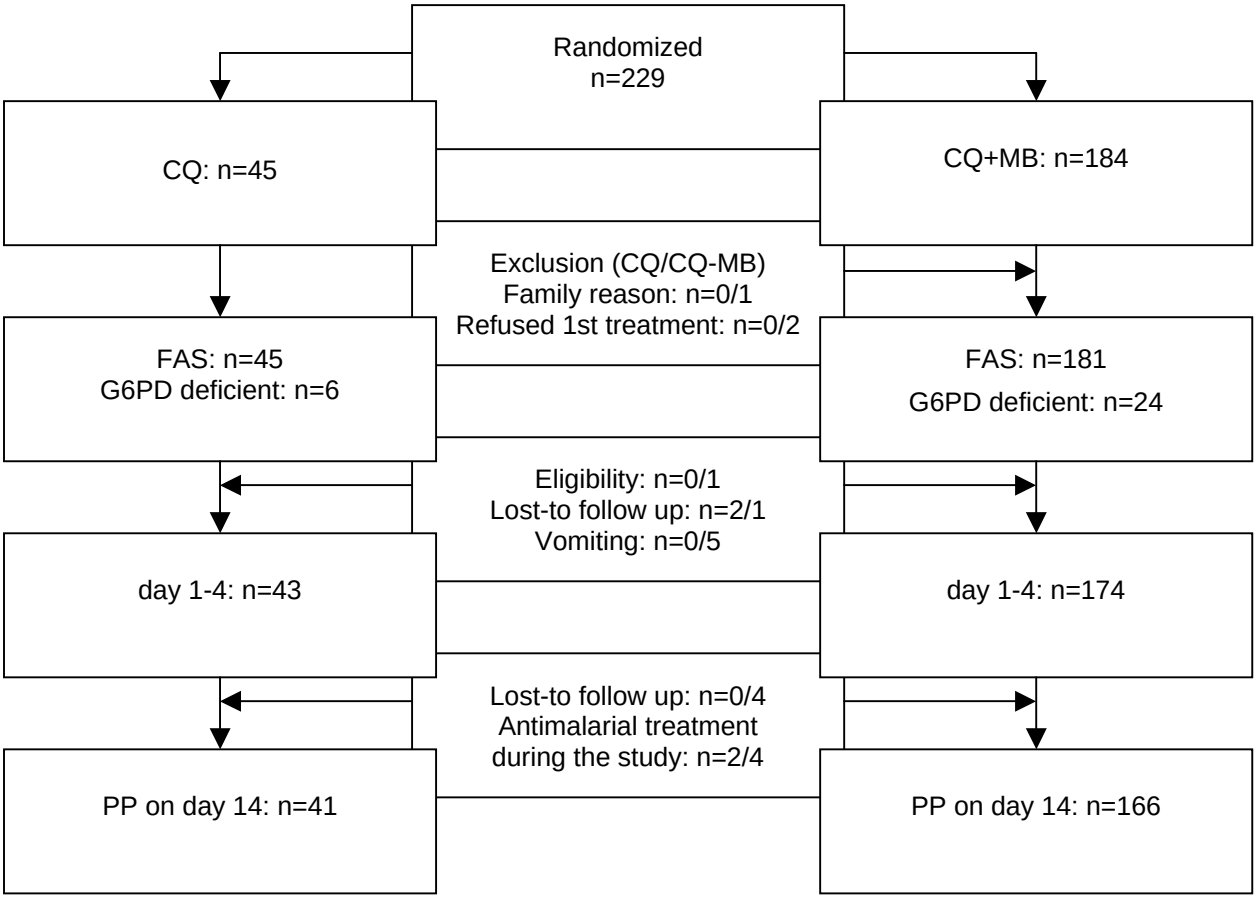

Figure 7-2: Flow chart of patients

7.3 Quality of Data

Double data entry was performed in Heidelberg. Inconsistencies were checked generating queries. The two investigators solved all queries. The data base was closed on the 26th of April 2004. The database was reopened on the 29th of April 2004, the 7th of May 2004, and the 7th of June 2004 to change a creatinine value and some dates/times for fever measurements. The necessary changes were discovered during analyzing the data. A physician from Ouagadougou monitored the trial data, no major problems occurred. The final analysis run in March 2005.

7.4 Demographic characteristics of study subjects

The mean age was 29.6 +/– 14.5 months (range: 6 to 59). The average weight was 10.6 +/– 2.8 kg (range: 5 to 22). In total there were 30 (13.3%) children with G6PD deficiency (modified Beutler-Mitchell-Test) and 171 (77%) patients with a (potential) genetic resistance for CQ. The two groups were comparable, the randomization was successful (Table 12-3). The current disease episode was 4.0 +/– 5.2 days (median: 3, range: 0 to 30). Nearly half of the children were treated before they were included in the trial, slightly more in the CQ group than in the CQ-MB group, 37.8% and 46.4% respectively (p_{CHI}=0.2948, Table 12-4).

7.5 Laboratory baseline data

Mean haemoglobin [g/dl] at baseline was 10.4 +/– 1.4 (range: 8.0 to 14.2), mean haematocrit [%] was 29.1 +/– 3.2 (range: 22 to 38), mean creatinine [µmol/l] was 76.8 +/– 14.6 (range: 27.7 to 127.4). The median parasite density (P. faliciparum) was 23000 (range: 1200 to 508000) with 4.33 +/– 0.54 (median: 4.36, range: 3.08 to 5.71) on the log10 scale (Table 12-6). 18/226 children had an additional infection with P. malariae. There were no major differences between the two treatment groups.

7.6 Prior medication

According to the caretakers self-reported information (N=226) more children from Nouna town (50/173, 28.9%) compared to those living in the villages (7/53, 13.2%) had received an antimalarial treatment with western drugs (>80% CQ) in the last 7 days prior to recruitment into the study, p_{Chi}=0.021.

Initial CQ drug levels were determined in 196 patients from filter paper according to Rengelshausen et al. 2004. Overall 32/196 (16.3%) had CQ in their blood (min 54 ng/ml,

median 267 ng/ml, max 2430 ng/ml], when presenting to the clinic. 31/143 (21.7%) children were from Nouna town, and 1/53 (1.9%) from the villages, (p_{Chi}= 0.0009).

7.7 Primary endpoint

Haemolysis: In the CQ-MB group there are 24 G6PD deficient children in the FAS and 22 in the PP set using the modified Beutler-Mitchell test (Table 12-2), but 22 G6PD deficient children in the FAS and 21 in the PP set using the PCR method.

There were no cases of (acute life-threatening) haemolysis in the patients with G6PD deficiency leading to an estimated incidence of 0% with an exact one-sided 95% confidence interval [0%, 11.7%] in the FAS (N=24) or [0%, 12.7%] in PP (N=22). Using the PCR results for the G6PD status the confidence intervals are [0%, 12.7%] for the FAS (N=22) and [0%, 13.3%] for the PP set (N=21), Table 12-27 to Table 12-30.

All upper margins are lower than 20%. The hypothesis (H_0: $p \geq 0.2$) can be rejected. The second primary parameter can therefore be tested hierarchically.

Combining these results with the pilot study in adult males (Mandi et al. 2005) we observed no haemolysis in 98 G6PD deficient subjects under CQ-MB. This updates the risk estimate to 3% (upper confidence bound).

Serious adverse events: One patient in the G6PD sufficient CQ-MB group had a serious adverse event (SAE; prolonged hospitalisation) which was unrelated to the study medication. The haemoglobin of this 21 months old girl with an initially high parasitaemia of 193000/µl and haemorrhagic diarrhoea dropped within 4 days from 11.8g/dl to 6.6g/dl. There was no need for blood transfusion. With quinine and antibiotics she quickly recovered within 5 days after admission to hospital. Due to sparse data there is no valid estimate of the relative risk, which is very close to 1 anyway (δ=1.0056). We used Fishers exact test instead (p_{FISHER}=1.0). There is no evidence for a different incidence of adverse events so far. But further studies are needed.

7.8 Efficacy analysis

The analysis is based on the analysis plan. But there is a change in the definition of the efficacy parameter to fulfil the regulations of the WHO document from 2004, the used definitions are given in chapter 6.4. The analysis was done for FAS and PP. For the PP set the results are summarized in Table 7-1. All results can be found in the Appendix (Table 12-31 to Table 12-36).

Early treatment failures: There were 17/45 ETF in the CQ group and 55/181 in the CQ-MB group, OR=0.72, 95% CI [0.36, 1.42], p_{CHI}=0.439. The result in the PP set is similar, OR=0.71 [0.34; 1.45]. The main reason for being a ETF was "Fever(>=37,5°C) on D3 (WHO) and parasite count > 0".

Late clinical failures: There were 9/45 LCF in the CQ group and 33/181 in the CQ-MB group, OR=0.89, 95% CI [0.39, 2.03], p_{CHI}=0.953. The result in the PP set is similar, OR=0.86 [0.34; 2.16]. The main reason for being LCF was "Fever(>=37,5°C) and parasite count > 0 on D4-D14 (WHO)".

Treatment failures: There were 26/45 TF in the CQ group and 88/181 in the CQ-MB group, OR=0.69, 95% CI [0.36, 1.34], p_{CHI}=0.351. The result in the PP set is similar, OR=0.68 [0.34; 1.35].

Late parasitological failures: There were 5/45 LPF in the CQ group and 21/181 in the CQ-MB group, OR=1.05, 95% CI [0.37, 2.96], p_{CHI}=1. The result in the PP set is similar, OR=1.04 [0.37; 29.5].

No difference between CQ and CQ-MB can be shown with this study but the point estimates of the CQ-MB group are better than in the CQ group (the smaller the OR the better CQ-MB).

Table 7-1: Efficacy parameter: ETF, LCF, TF, LPF (PP set)

Parameter	CQ (N=41)	CQ-MB (N=166)
ETF	15 (36.6%)	48 (28.9%)
OR, 95% CI, p-Value	OR=0.705, [0.34; 1.45], p_{CHI}=0.444	
LCF	7 (17.1%)	25 (15.1%)
OR, 95% CI, p-Value	OR=0.861, [0.34; 2.16], p_{CHI}=0.938	
TF (ETF or LCF)	22 (53.7%)	73 (44.0%)
OR, 95% CI, p-Value	OR=0.678, [0.34; 1.35], p_{CHI}=0.348	
LPF	5 (12.2%)	21 (12.6%)
OR, 95% CI, p-Value	OR=1.043, [0.37; 2.95], p_{CHI}=1.000	
TF or LPF	27 (65.9%)	94 (56.6%)
OR, 95% CI, p-Value	OR=0.677, [0.331; 1.384], p_{CHI}=0.370	

continuity adjusted Chi-square-Test

Children-analysis: Categorizing the children using the age (<2years and ≥2years) the results in both groups are quite similar looking at the TF (Table 12-33, Table 12-34), no interaction can be shown (logistic regression, test of interaction group*young, p=0.674 in the FAS population, p=0.589 in the PP population).

Clinical resistance analysis: Most children were recruited from Nouna town (N=173), but some came from the villages around Nouna (N=53). The rate of TF in the CQ group is 22/34 (64.7%) in the children from Nouna town and 4/11 (36.4%) from villages respectively. Therefore less children from villages were clinically CQ-resistant. Statistically this cannot be confirmed (p_{CHI}=0.193) due to a low sample size. The origin (town or village) and treatment group interaction is testing the hypothesis whether the children from villages have more or less profit from methylene-blue. This cannot be concluded by the data (logistic regression, test of interaction group*origin, p=0.252 in the FAS population, p=0.704 in the PP population). That is due to the fact that about the same difference is found for the CQ-MB group as for the CQ group: 82/139 children from Nouna town are TF (59.0%) but only 6/42

patients from the villages (14.3%), (p_{CHI}<0.0001, FAS population). All given p-values can only be used descriptively.

7.9 Fever and parasite clearance time

Fever was measured several times during hospitalization but not between day5 and day14, only in cases when the patient comes irregularly to the hospital due to fever. However, the median fever clearance can be estimated due to the fact that the fever decreases quickly below 37.5°C (the two lower curves in Figure 7-3). But the parasites (the two upper curves in Figure 7-3) decrease slower (event: no parasitaemia, parasite count = 0). The estimated curve for fever favours slightly the CQ group, but p_{WMW}=0.347. The estimated curve for parasite clearance favours CQ-MB, but p_{WMW}=0.274 (Table 12-37). About the same results are given for the PP set (Table 12-38). More detailed information about the fever flow is given in Table 12-22 to Table 12-25.

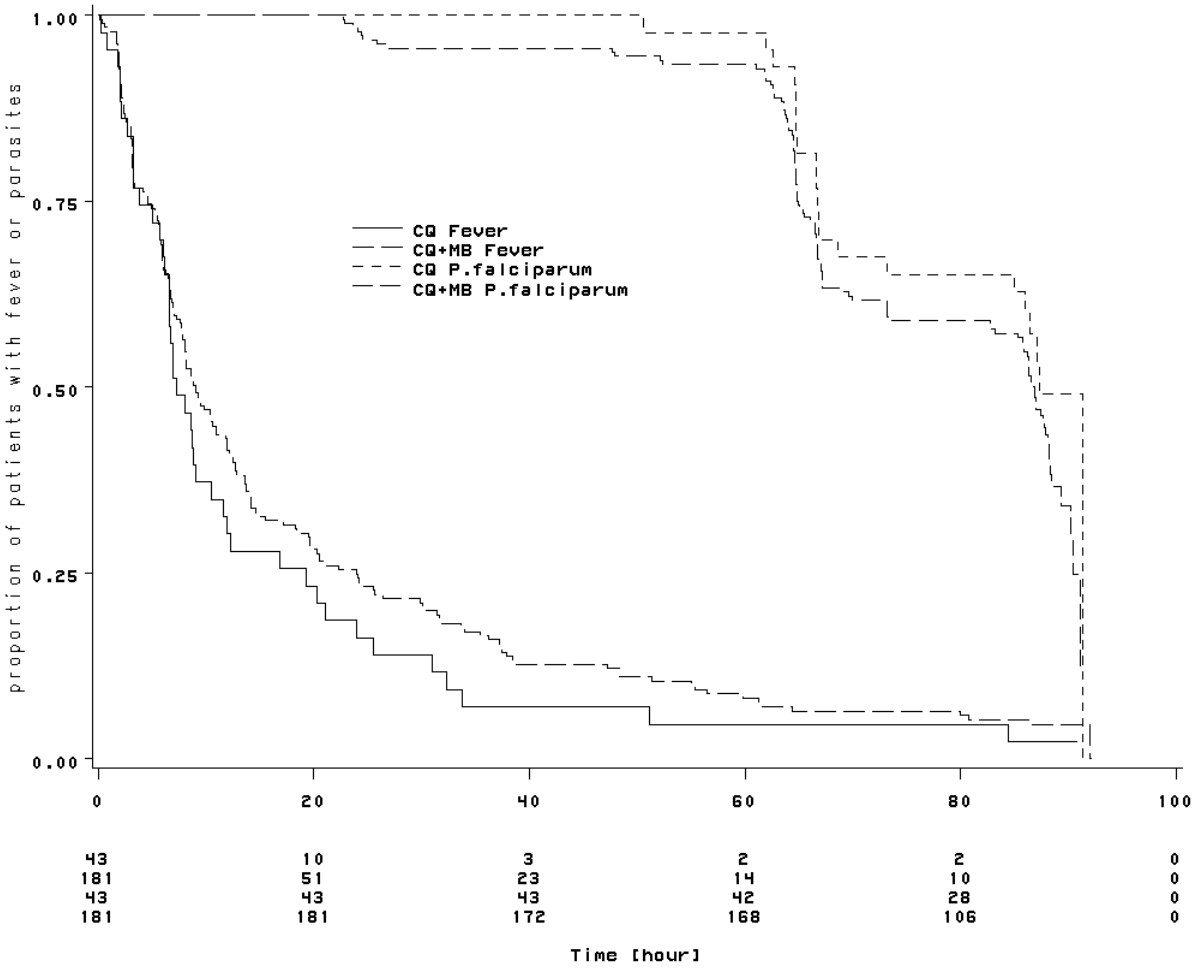

Figure 7-3: Kaplan-Meier curves for fever and parasites by treatment group

7.10 Laboratory follow-up

The Laboratory results of the CQ and CQ-MB group by WHO days (D0 - D14) are given in Table 12-10, Table 12-12, Table 12-14, Table 12-15, Table 12-18, and Table 12-19. The Laboratory results of the CQ and CQ-MB group by study/calendar days (day 1 - day 14) are given in Table 12-11, Table 12-13, Table 12-16, Table 12-17, Table 12-20, and Table 12-21. In the following only calendar days are used for the analysis of laboratory data. The blood was taken on different time points in order to analyse population kinetics. Therefore data might be shifted one day and the sample size is slightly smaller than expected. In case of calendar days e.g. CQ on day 4: N=33 instead of N=45, CQ-MB on day 4: N=140 instead of N=181. In case of WHO days e.g. CQ on day 4: N=38 instead of N=45, CQ-MB on day 4: N=164 instead of N=181.

In the CQ group a slight decrease in haemoglobin [g/dl] of –0.2 +/– 1.3 with a 95% confidence interval of [–0.7, 0.2] was observed over the three days (Table 12-16). In the CQ-MB group a decrease in haemoglobin [g/dl] of –0.4 +/– 1.6 with a 95% confidence interval of [–0.6, –0.1] was observed over the three days (Table 12-20). The decrease is not different in both groups (p_{WMW}=0.935).

In the CQ group no change in haematocrit [%] (–0.1 +/– 3.0, [–1.1, 1.0]) was observed over the three days (Table 12-16). In the CQ-MB group a decrease in haematocrit [%] of –1.0 +/– 3.1 with a 95% confidence interval of [–1.5, –0.5] was observed over the three days (Table 12-20). The change in haematocrit does not seem to be different in both groups (p_{WMW}=0.139).

Table 7-2: Change in Hb and Hct from baseline to day 4 by G6PD status (CQ-MB)

	G6PD deficient	G6PD sufficient
Haemoglobin [g/dl]		
N	18	119
Mean +/– SD	–0.4 +/– 1.2	–0.3 +/– 1.7
95% CI mean	[–1.0; 0.2]	[–0.6; –0.0]
Haematocrit [%]		
N	18	119
Mean +/– SD	–1.4 +/– 2.8	–0.9 +/– 3.1
95% CI mean	[–2.8; –0.0]	[–1.4; –0.3]

The G6PD status was evaluated by PCR; G6PD status for 3 children is missing.

The primary endpoint was evaluated in the G6PD deficient children. Regarding the Changes in Hb and Hct there seems to be no difference between deficient and sufficient children within the CQ-MB group ($p_{WMW} = 0.662$ and $p_{WMW} = 0.408$ respectively), Table 7-2.

The correlation between haemoglobin and haematocrit at baseline is poor (r=0.57). We also calculated a linear regression of haemoglobin on haematocrit in order to investigate whether one can simply measure Hct instead of Hb (Hb = 3.294 + 0.243 Hct). Only r^2=33% of the variability of Hb can be explained using the linear model with Hct as a independent variable. Figure 7-4 shows the scatter-plot with the 95% prediction interval, e.g. with Hct=30% the predicted Hb value is 10.6g/dl with a 95% prediction interval of [8.3; 12.8]. Only measuring the Hct instead of Hb cannot be recommended. (Note: Without an intercept the fitted linear model is Hb = 0.355 Hct.)

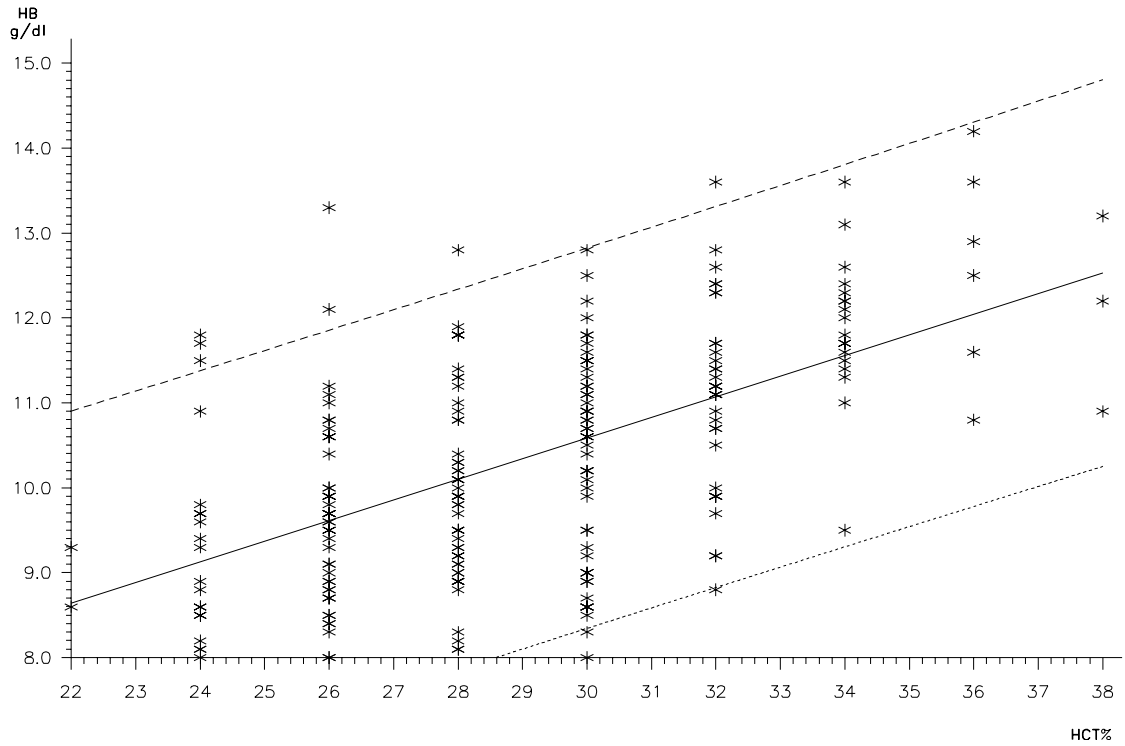

Figure 7-4: Regression of haemoglobin on haematocrit

Creatinine was measured at baseline, day 3 and day 4 (D0, D2, D3). In the CQ group there is no change from baseline to day 4 (D3) (0.4 +/– 15.2, [–5.0; 5.7]) but in the CQ-MB group was a decrease in creatinine (–2.4 +/– 13.8, [–4.7; –0.1]). Nevertheless, the difference cannot be shown statistically (p_{WMW} = 0.423) (Table 12-16, Table 12-20), see also Figure 11-7 and Figure 11-8.

7.11 Concomitant medication

There was no major difference in the intake of concomitant medication during the trial regarding antibiotics (27.7% vs. 33.8%), antihistaminic (4.2% vs. 1.3%), additional antimalarial drugs (24.4% vs. 22.3%), antipyretics (31.1% vs. 29.6%), or others (12.6% vs. 13.1%), see Table 12-26.

7.12 Safety analysis

For the safety analysis all 226 children were considered. Only one serious adverse events was reported, see chapter 7.6.

74.8% of the patients had at least one reported adverse event, 73.3% in CQ group and 75.1% in the CQ-MB group: In total 284 adverse events were reported. Only 2 AEs were severe (0.7%), all others mild (50.4%) or moderate (48.9%), Table 12-41.

The type of Adverse events were mainly gastrointestinal or respiratory disorders or infections (Table 7-3). But no major difference between groups can be seen. The only remarkable SOC is "skin and subcutaneous tissue disorders" with a higher rate in the CQ group (p_{FISHER}=0.0125), but the children in CQ-MB got the same dosage of CQ. This difference therefore happened probably by chance because it is not likely that MB is protective regarding "skin and subcutaneous tissue disorders".

Table 7-3: Adverse events by group and MedDRA SOC term

	CQ (N=45)	CQ-MB (N=181)	Total (N=226)
Patients with at least one AE	33 (73.3%)	136 (75.1%)	169 (74.8%)
Number of AE's (=100%)	60 (100.0%)	224 (100.0%)	284 (100.0%)
MedDRA SOC			
- Gastrointestinal disorders	23 (38.3%)	93 (41.5%)	116 (40.8%)
- Respiratory, thoracic and mediastinal disorders	16 (26.7%)	78 (34.8%)	94 (33.1%)
- Infections and infestations	10 (16.7%)	38 (17.0%)	48 (16.9%)
- Skin and subcutaneous tissue disorders	8 (13.3%)	9 (4.0%)	17 (6.0%)
- Nervous system disorders	1 (1.7%)	4 (1.8%)	5 (1.8%)
- Hepatobiliary disorders	0 (0.0%)	2 (0.9%)	2 (0.7%)
- Metabolism and nutrition disorders	1 (1.7%)	0 (0.0%)	1 (0.4%)
- Psychiatric disorders	1 (1.7%)	0 (0.0%)	1 (0.4%)

7.13 Acceptance of MB intake

Overall acceptance of the MB treatment was excellent, despite staining of clothes associated with urinating children. There was no response from 4/181 caretakers, 94/181 of the caretakers had no problem with the CQ-MB treatment, while 83/181 caretakers mentioned minor difficulties concerning the washing procedure of the stained clothes. However, all said that they would give CQ-MB again to their children if they became sick (Table 12-39).

7.14 Quality of Beutler-Mitchell-Test

For 222 patients two G6PD tests were available. Assuming the PCR results for the G6PD status as the gold-standard one could estimate the sensitivity and specificity and their

asymptotic 95% confidence intervals as quality parameters for the Beutler-Mitchell-Test: Sensitivity 25/29 = 0.862 [0.739, 0.933], specificity 188/193 = 0.974 [0.956, 0.985] (Table 12-5). In conclusion the Beutler-Mitchell-Test gives a high specificity with a low number of false positive results, the test could be used to confirm the G6PD deficiency. The estimate for the sensitivity is lower than 90%. In general this is too low for a screening test.

Another analysis without a gold standard (both diagnostic tests have equal rights) will be published elsewhere.

7.15 genetic resistance to CQ

The prevalence of the genetic resistance (pfcrt T76) is 76% in CQ group and 77% in the CQ-MB group (Table 12-3). Furthermore the prevalence of the genetic resistance is 81% in Nouna town and 64% in children from the villages (OR=2.39 [1.21, 4.73], p_{Chi}=0.0106).

Due to the fact that only 45 patients in the CQ group and 53 patients from rural area can be analysed, the methods of analyzing interactions have very low statistical power. The final model (TF as outcome parameter) contains the three single covariates (treatment group, regional provenance, genetic resistance) and the interaction of treatment group and regional provenance. In the rural area might be therefore the treatment effect (difference between CQ and CQ-MB) different of the effect in Nouna town.

Analyzing the data post hoc by regional provenance no group effect (town p=0.5663, rural p=0.0562) nor an effect of the genetic resistance (town p=0.1087, rural p=0.1359) can be shown. For exploratory purposes the odds ratio is 5.1 [0.958; 27.509] in favour of the CQ-MB treatment in the rural area but only 1.3 [0.573; 2.77] in Nouna town.

Analyzing the data post hoc by treatment group the provenance (p<0.0001) as well as the resistance (p=0.0272) seems to have an impact on TF in the CQ-MB group: Children from the rural area and/or with parasites without the pfcrt resistance have a better prognosis. Those effects can not be confirmed by the CQ group (p=0.1711, p=0.7423 respectively) which supports the interaction. Further details will be published elsewhere.

8 Discussion

MB has been used systematically against malaria in different human populations during the late 19th and the early 20th century, but the effects of this drug were poorly documented in these old studies (Schirmer et al. 2003). This study provides the first data on the safety and efficacy of methylene blue in young children with falciparum malaria in SSA. MB was

chosen to be applied in combination with CQ for reasons of expected synergy, and because combination therapy is the new paradigm in malaria therapy (White et al. 1999, Nosten and Brasseur 2002).

During treatment of 181 children including 24 G6PD deficient children with uncomplicated falciparum malaria in Burkina Faso, no drug related SAEs and particularly no cases of severe haemolysis were observed. This does not mean that SAEs can be excluded totally, but the likelihood is certainly smaller than the risk of young SSA children dying from malaria (Snow et al. 1999). Moreover, no other adverse events likely to be related to the study drugs were noted. Thus, the findings from this study for the first time demonstrate the safety of a methylene blue based combination in the treatment of malaria in young children of SSA. These results support previous findings on the safety of CQ-MB in G6PD sufficient or deficient adults in Europe and SSA (Rengelshausen et al. 2004, Mandi et al. 2005). Although there were no safety problems with the oral combination of CQ-MB, the administration of the bitter-tasting MB solution was sometimes difficult, especially in younger children. The formulation of MB will thus need improvement (e.g. by taste masking) before large-scale application.

The findings from this study show that MB appears to be safe at an oral dose of up to 4mg/kg/day over 3 days in SSA populations with dominating class III G6PD deficiency, despite its being on the list of drugs reported to potentially cause severe haemolysis in G6PD deficient populations (Fleming and Silva 2003). However, this listing at least in part may have its origin in falsely attributing haemolysis caused by the underlying infectious disease to the drug used for treatment (Beutler 1994). Nevertheless, as MB is an oxidant and G6PD has an important role in the elimination of reactive oxygen species in the erythrocyte the safety of MB may be influenced by the prevailing type of G6PD deficiency (Janssen et al. 2004). Further studies are needed in populations where G6PD deficiency class II occurs (Fleming and Silva 2003).

The combination of dapsone and chloroproguanil (Lapdap) has recently been registered for malaria therapy in SSA (Lang and Greenwood 2003). With regard to the potential of haemolysis development in G6PD deficient populations, MB belongs to the same risk category as dapsone (Fleming and Silva 2003). Thus our findings may also be reassuring the safety of Lapdap in SSA populations.

Compared to CQ resistance data from the surrounding villages, the observed rate of clinical failures during CQ treatment was surprisingly high in the urban/semi-urban population of this study (details will be published elsewhere) (Müller et al. 2003b). In most of Burkina Faso, the

level of resistance to CQ has remained remarkably stable during recent years (Ouedraogo et al. 1998; Tinto et al. 2002; Modiano et al. 2001). However, much higher CQ clinical failure rates were already documented from the capital town Ouagadougou (Sirima et al. 2003). A change in the first line treatment of uncomplicated malaria is currently under discussion in Burkina Faso.

The clinical failure rate was higher in the CQ arm (54%) compared to the CQ-MB arm (44%), but this difference was not significant. This result could possibly be explained by a too low dose of MB chosen in this study. Such an assumption is supported by much higher MB doses reported during treatment of malaria patients some 100 years ago (Ferreira 1893, Guttmann and Ehrlich 1891, Mayer 1919, Klemperer 1924). In one of these studies, 40 young children with malaria were safely treated in Brasil with oral doses of 20-50 mg/kg/day MB over several days to weeks (Ferreira 1893). However, in these old publications efficacy outcomes were often usually uncontrolled and poorly documented.

In this study, methylene blue was again well accepted by the population. Staining of clothes was not considered as a major problem by mothers. Only in a few cases 2-3 traditional washes were needed before stains were totally removed. All mothers in our study considered this point irrelevant compared to the health of their children. This confirms results from a former experimental study on the reversibility of MB stains in local clothes and supports findings from an anthropological study - on community perceptions of blue urine, blue eyes and blue clothes - conducted during the rainy season of the year 2003 in the rural Nouna study area (Sanou, unpublished data).

In conclusion, the combination CQ-MB has been shown to be safe for the treatment of uncomplicated falciparum malaria in young West African children with a high prevalence of G6PD deficiency. However, this combination was not sufficiently effective in the chosen dosage regimen. A dose finding study is under way to clarify if this combination is effective at higher doses of MB.

The following issues can be concluded for the future:

- Discussion about CQ as first line treatment of uncomplicated malaria is needed in Burkina Faso
- The formulation of MB needs improvement
- A dose finding study is necessary.
    - test higher doses of MB
    - use Hb (not only Hct) due to low prediction

- use current WHO guidelines and recommendations
- determine G6PD status for safety reasons

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11 Appendix: Figures

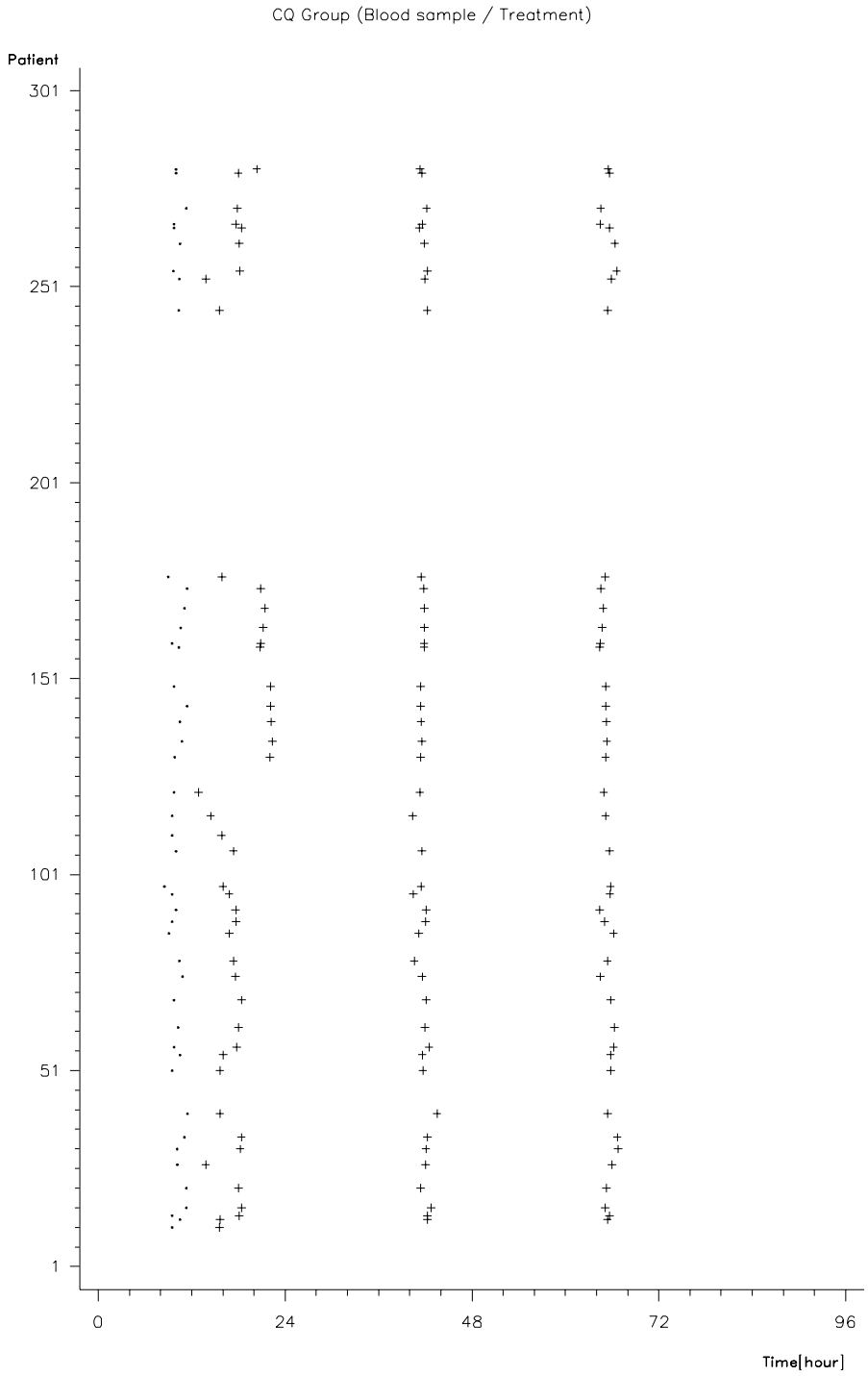

Figure 11-1: Baseline blood sample and treatment pattern by individual (CQ)

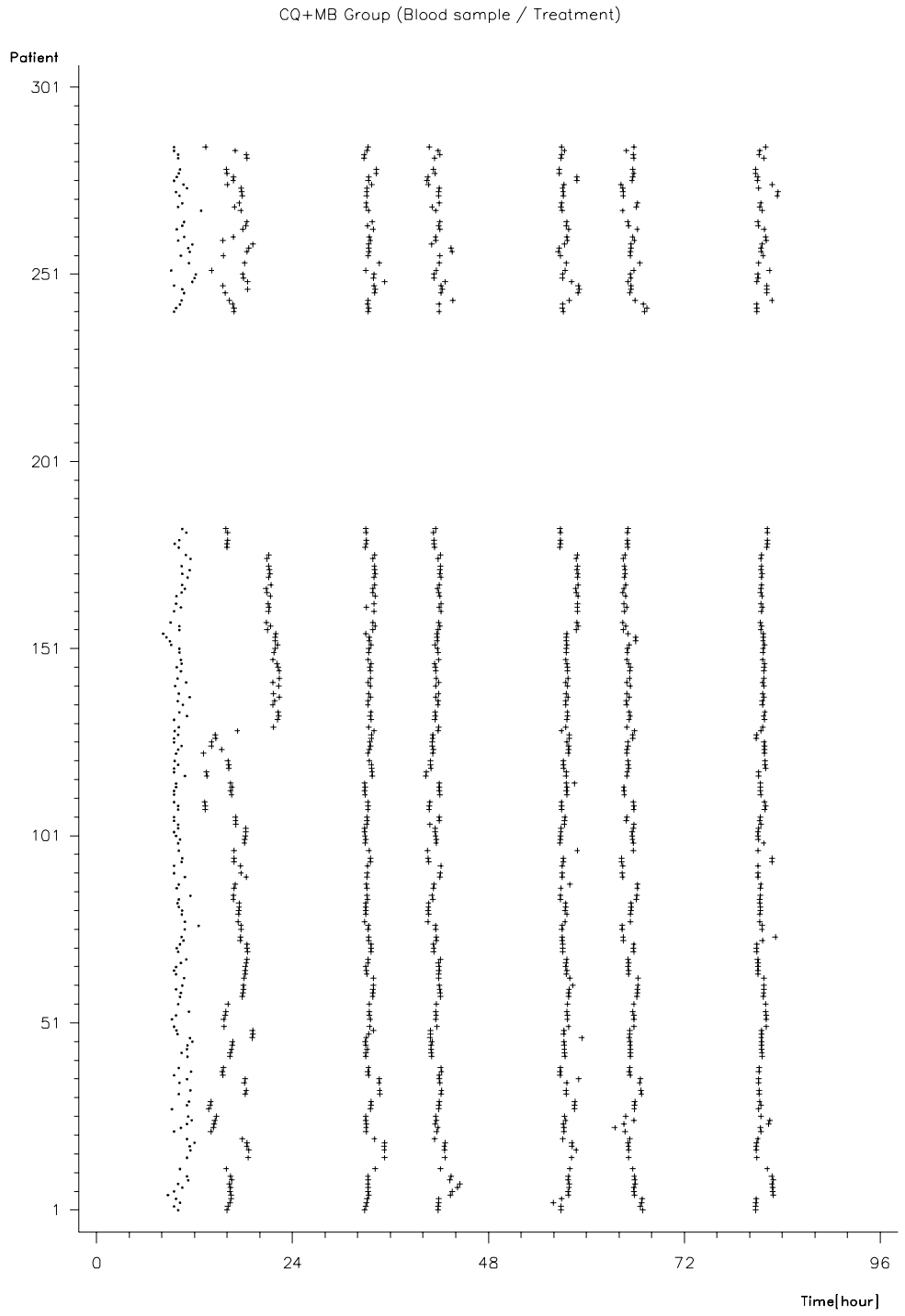

Figure 11-2: Baseline blood sample and treatment pattern by individual (CQ-MB)

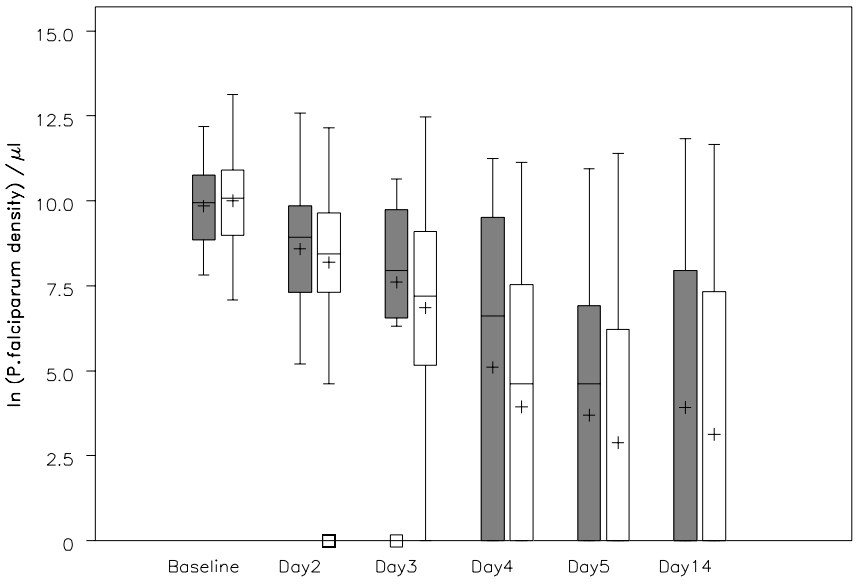

Figure 11-3: ln(parasite count) over time by group, calendar day

(grey=CQ, white=CQ-MB) s

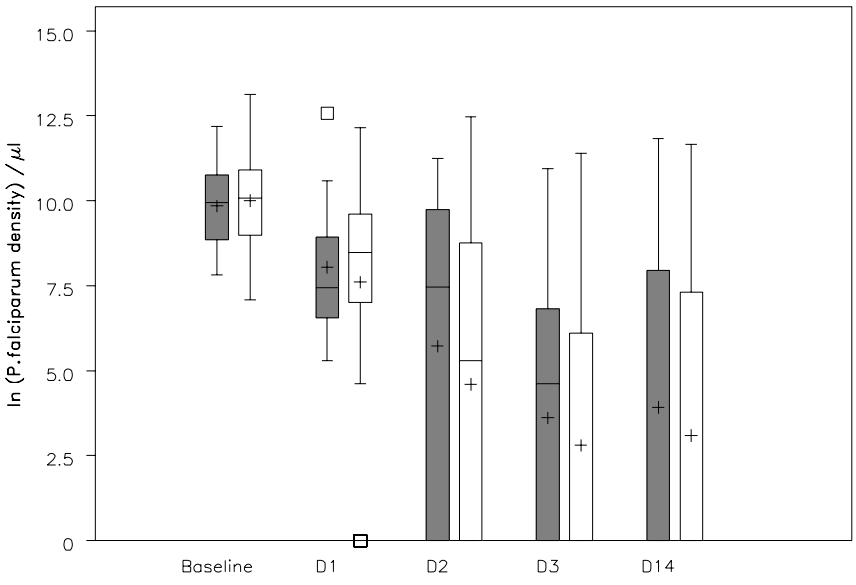

Figure 11-4: ln(parasite count) over time by group, WHO days

(grey=CQ, white=CQ-MB)

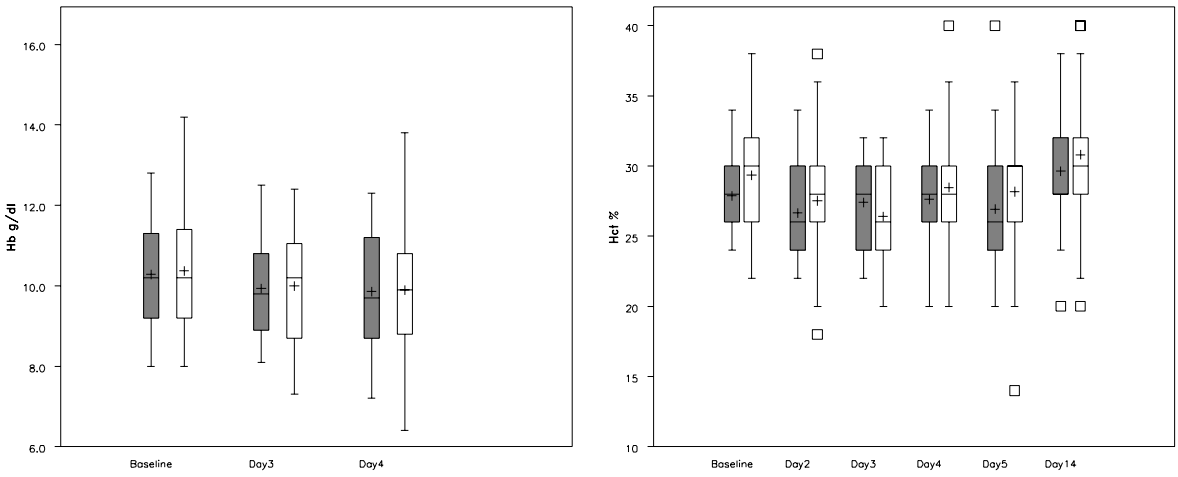

Figure 11-5: Hb and Hct values over time by group, calendar days

(grey=CQ, white=CQ-MB)

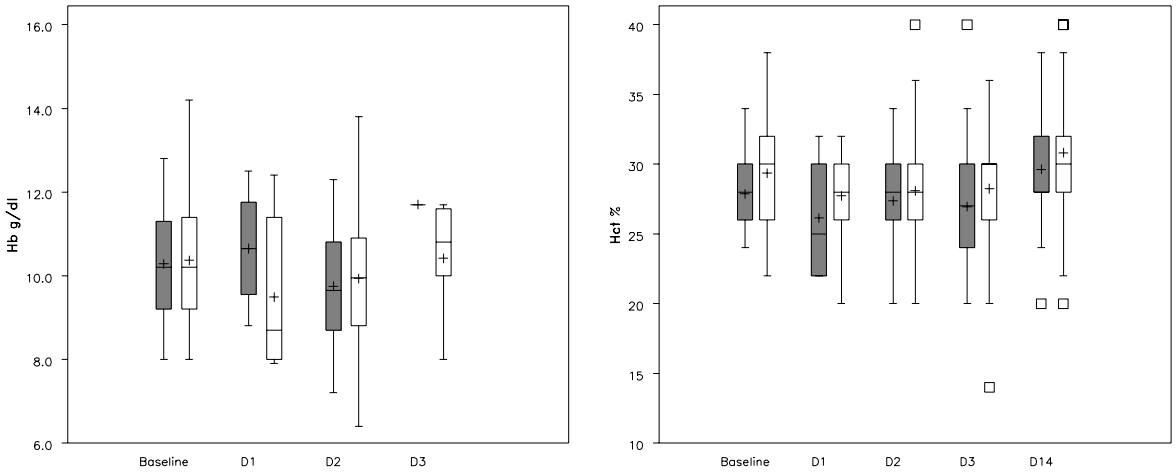

Figure 11-6: Hb and Hct values over time by group, WHO days

(grey=CQ, white=CQ-MB)

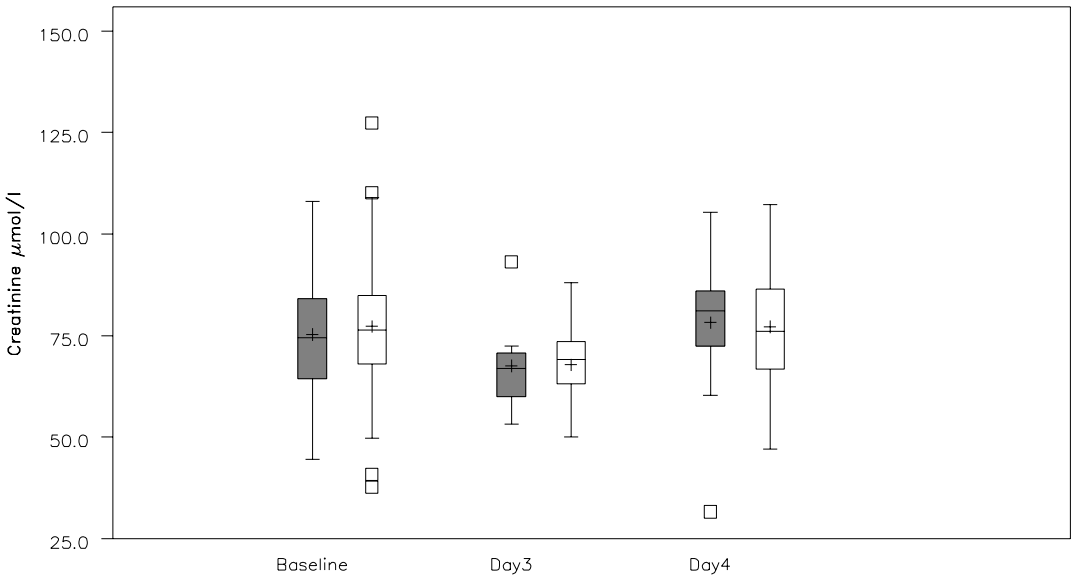

Figure 11-7: Creatinine values over time by group, calendar days

(grey=CQ, white=CQ-MB)

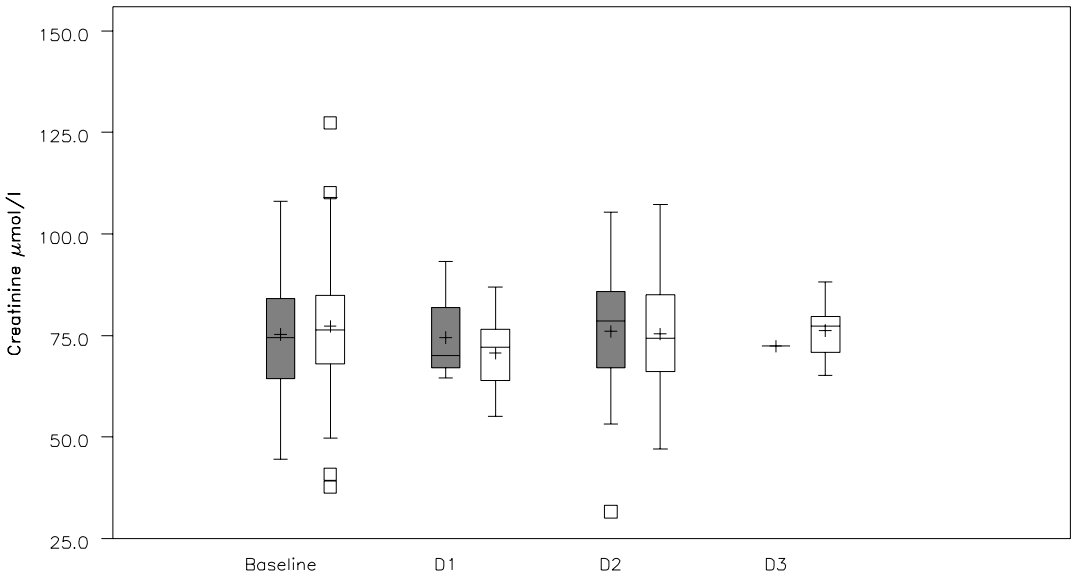

Figure 11-8: Creatinine values over time by group, WHO days

(grey=CQ, white=CQ-MB)

12 Appendix: Tables

Table 12-1: Recruiting of patients (FAS)

Week	from – to	N	N(%)cumulative
1	13/10/2003 - 19/10/2003	43	43(19.0%)
2	20/10/2003 - 26/10/2003	54	97(42.9%)
3	27/10/2003 - 02/10/2003	39	136(60.2%)
4	03/11/2003 - 09/11/2003	32	168(74.3%)
5	10/11/2003 - 16/11/2003	31	199(88.1%)
6	17/11/2003 - 23/11/2003	27	226(100.0%)

Table 12-2: Analysis sets and protocol compliance

	CQ N(%)	CQ+MB N(%)	Total N(%)
Included pat. (informed consent)	45(100.0%)	184(100.0%)	229(100.0%)
- Pat. without trial medication	0(0.0%)	3(1.6%)	3(1.3%)
Pat. in FAS	45(100.0%)	181(98.4%)	226(98.7%)
- Pat. not treated per protocol	2(4.4%)	1(0.5%)	3(1.3%)
- Pat.who vomited and the drug was not given again or it's unclear whether it was given again	0(0.0%)	5(2.7%)	5(2.2%)
- Pat.who violate inclusion/exclusion criteria	0(0.0%)	1(0.5%)	1(0.4%)
- Pat. without blue urine		0(0.0%)	45(19.7%)
- Lost to follow-up	0(0.0%)	4(2.2%)	4(1.7%)
- treated (D4-D13) with antimalarials although no fever and/or no parasites	2(4.4%)	4(2.2%)	6(2.6%)
Pat. in PP set	41(91.1%)	166(90.2%)	207(90.4%)
- Pat. G6PD sufficient	35(77.8%)	144(78.3%)	179(78.2%)
Pat. in PP and G6PD deficient	6(13.3%)	22(12.0%)	28(12.2%)
Pat. in FAS	45(100.0%)	181(98.4%)	226(98.7%)
- Pat. G6PD sufficient	39(86.7%)	157(85.3%)	196(85.6%)

% are based on all included patients

Table 12-3: Demographics by group (FAS)

Characteristic	CQ (N=45)	CQ-MB (N=181)	Total (N=226)
Sex			
- male	36(80.0%)	145(80.1%)	181(80.1%)
- female	9(20.0%)	36(19.9%)	45(19.9%)
Age [months]			
- N	45	181	226
- Mean +/- SD	30.0+/-13.1	29.5+/-14.9	29.6+/-14.5
- Median	28.0	27.0	27.5
- Min, Max	7.0, 55.0	6.0, 59.0	6.0, 59.0
Weight [kg]			
- N	45	181	226
- Mean +/- SD	10.5+/- 2.8	10.6+/- 2.8	10.6+/- 2.8
- Median	10.0	10.0	10.0
- Min, Max	5.0, 17.0	5.5, 20.0	5.0, 20.0
Chronic Illness			
- No	45(100.0%)	179(98.9%)	224(99.1%)
- Yes	0(0.0%)	2(1.1%)	2(0.9%)
G6PD deficiency (1)			
- No	39(86.7%)	157(86.7%)	196(86.7%)
- Yes	6(13.3%)	24(13.3%)	30(13.3%)
resistance (mutation pfcrt T76)			
- No	11(24.4%)	40(22.6%)	51(23.0%)
- Yes	34(75.6%)	137(77.4%)	171(77.0%)
- Missing	0	4	4

(1) modified Beutler-Mitchell-Test

Table 12-4: Demographics by group (FAS)

Characteristic	CQ (N=45)	CQ-MB (N=181)	Total (N=226)
Length of current disease episode[days]			
- N	44	176	220
- Mean +/- SD	3.7+/- 4.7	4.0+/- 5.3	4.0+/- 5.2
- Median	3.0	3.0	3.0
- Min, Max	1.0, 30.0	0.0, 30.0	0.0, 30.0
Prior treatment of current disease episode			
- No	28(62.2%)	97(53.6%)	125(55.3%)
- Yes	17(37.8%)	84(46.4%)	101(44.7%)
Treatment of current disease episode			
- Antipyretic	10(58.8%)	30(35.7%)	40(39.6%)
- Chloroquin + Antipyretic	4(23.5%)	21(25.0%)	25(24.8%)
- Chloroquin	1(5.9%)	18(21.4%)	19(18.8%)
- Unknown	2(11.8%)	4(4.8%)	6(5.9%)
- Traditional	0(0.0%)	4(4.8%)	4(4.0%)
- Antipyretic + Amoxillin	0(0.0%)	2(2.4%)	2(2.0%)
- Quinin	0(0.0%)	2(2.4%)	2(2.0%)
- Amodiaquin	0(0.0%)	1(1.2%)	1(1.0%)
- Antipyretic + Amodiaquin	0(0.0%)	1(1.2%)	1(1.0%)
- Chloroquin + Cotrimoxazol + Antipyretic	0(0.0%)	1(1.2%)	1(1.0%)

Table 12-5: G6PD deficiency (Beutler-Mitchell test vs. PCR test) (FAS)

Characteristic	PCR (negative)	PCR (positive)	Total
Beutler-Mitchell (negative)	188	4	192
Beutler-Mitchell (positive)	5	25	30
Total	193	29	222

Table 12-6: Baseline laboratory by group (FAS)

Characteristic	CQ (N=45)	CQ+MB (N=181)	Total (N=226)
Haemoglobin[g/dl]			
- N	45	181	226
- Mean +/- SD	10.3+/- 1.3	10.4+/- 1.4	10.4+/- 1.4
- Median	10.2	10.2	10.2
- Min, Max	8.0, 12.8	8.0, 14.2	8.0, 14.2
Haematocrit[%]			
- N	45	181	226
- Mean +/- SD	27.9+/- 2.6	29.4+/- 3.3	29.1+/- 3.2
- Median	28.0	30.0	28.0
- Min, Max	24.0, 34.0	22.0, 38.0	22.0, 38.0
Creatinine[µmol/l]			
- N	45	181	226
- Mean +/- SD	75.3+/- 15.2	77.2+/- 14.5	76.8+/- 14.6
- Median	74.4	76.4	75.3
- Min, Max	44.5, 108.0	37.7, 127.4	37.7, 127.4
log10(P. falciparum)[/µl]			
- N	45	181	226
- Mean +/- SD	4.28+/-0.54	4.35+/-0.54	4.33+/-0.54
- Median	4.32	4.38	4.36
- Min, Max	3.40, 5.29	3.08, 5.71	3.08, 5.71
P. ovale[/µl]			
- N	45	181	226
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
P. malariae[/µl]			
- N	45	181	226
- Mean +/- SD	304.4+/- 1655.0	2308.8+/- 17528.6	1909.7+/- 15715.6
- Median	0.0	0.0	0.0
- Min, Max	0.0, 11000.0	0.0, 180000.0	0.0, 180000.0

Table 12-7: Baseline laboratory by group (FAS)

Characteristic	CQ (N=45)	CQ+MB (N=181)	Total (N=226)
Haemoglobin[g/dl]			
- N	45	181	226
- Mean +/- SD	10.3+/- 1.3	10.4+/- 1.4	10.4+/- 1.4
- Median	10.2	10.2	10.2
- Min, Max	8.0, 12.8	8.0, 14.2	8.0, 14.2
Haematocrit[%]			
- N	45	181	226
- Mean +/- SD	27.9+/- 2.6	29.4+/- 3.3	29.1+/- 3.2
- Median	28.0	30.0	28.0
- Min, Max	24.0, 34.0	22.0, 38.0	22.0, 38.0
Creatinine[µmol/l]			
- N	45	181	226
- Mean +/- SD	75.3+/- 15.2	77.2+/- 14.5	76.8+/- 14.6
- Median	74.4	76.4	75.3
- Min, Max	44.5, 108.0	37.7, 127.4	37.7, 127.4
log10(P. falciparum)[/µl]			
- N	45	181	226
- Mean +/- SD	4.28+/-0.54	4.35+/-0.54	4.33+/-0.54
- Median	4.32	4.38	4.36
- Min, Max	3.40, 5.29	3.08, 5.71	3.08, 5.71
P. ovale[/µl]			
- N	45	181	226
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
P. malariae[/µl]			
- N	45	181	226
- Mean +/- SD	304.4+/- 1655.0	2308.8+/- 17528.6	1909.7+/- 15715.6
- Median	0.0	0.0	0.0
- Min, Max	0.0, 11000.0	0.0, 180000.0	0.0, 180000.0

Table 12-8: Compliance by group (FAS)

	CQ (N=45)	CQ+MB (N=181)
Number of Pat. with drug intake (1)		
- Day1	45(100.0%)	181(100.0%)
- Day1, Day2	43(95.6%)	181(100.0%)
- Day1, Day2, Day3	43(95.6%)	181(100.0%)
- Day1, Day2, Day3, Day4	-	180(99.4%)
Blue urine at least once		
- Yes	0(0.0%)	181(100.0%)
- No	45(100.0%)	0(0.0%)
Time to treatment[hour]		
- N	45	181
- Mean +/- SD	7.8+/-2.3	7.4+/-2.5
- Median	7.7	7.0
- p5, p25, p75, p95	3.6, 6.5, 8.7, 11.7	3.7, 5.9, 8.5, 12.0
- Min, Max	3.1, 12.4	2.7, 13.8

Table 12-9: Laboratory findings by group and G6PD status (FAS)

	G6PD sufficient patients		G6PD deficient patients		all patients	
Characteristic	CQ	CQ-MB	CQ	CQ-MB	CQ	CQ-MB
Haemoglobin [g/dl]						
at Baseline						
- N	38	155	7	22	45	181
- Mean +/- SD	10.4 +/- 1.3	10.3 +/- 1.4	9.5 +/- 0.9	10.6 +/- 1.6	10.3 +/- 1.3	10.4 +/- 1.4
- 95% CI mean	[10.0; 10.9]	[10.1; 10.6]	[8.7; 10.3]	[9.9; 11.2]	[9.9; 10.7]	[10.2; 10.6]
Change in Haemoglobin [g/dl]						
Day4-Baseline *						
- N	27	119	6	18	33	140
- Mean +/- SD	-0.4 +/- 1.2	-0.3 +/- 1.7	0.9 +/- 1.3	-0.4 +/- 1.2	-0.2 +/- 1.3	-0.4 +/- 1.6
- 95% CI mean	[-1.0; -0.0]	[-0.6; -0.0]	[-0.4; 3.4]	[-1.0; 0.2]	[-0.7; 0.2]	[-0.6; -0.1]
Haematocrit[%]						
at Baseline						
- N	38	155	7	22	45	181
- Mean +/- SD	27.7 +/- 2.6	29.1 +/- 3.3	28.6 +/- 3.0	30.8 +/- 3.4	27.9 +/- 2.6	29.4 +/- 3.3
- 95% CI mean	[26.9; 28.6]	[28.6; 29.6]	[25.8; 31.3]	[29.3; 32.3]	[27.1; 28.7]	[28.9; 29.8]
Change in Haematocrit[%]						
Day4-Baseline *						
- N	27	119	6	18	33	140
- Mean +/- SD	-0.1+/- 3.1	-0.9 +/- 3.1	0.3 +/- 2.9	-1.4 +/- 2.8	-0.1 +/- 3.0	-1.0 +/- 3.1
- 95% CI mean	[-1.4; 1.1]	[-1.4; -0.3]	[-2.8; 3.4]	[-2.8; -0.0]	[-1.1; 1.0]	[-1.5; -0.5]
Change in Haematocrit[%]						
Day4-Baseline						
- N	36	155	7	22	43	180
- Mean +/- SD	-1.2 +/- 2.8	-1.0 +/- 4.1	0.8 +/- 4.0	-1.5 +/- 3.8	-0.9 +/- 3.1	-1.2 +/- 4.0
- 95% CI mean	[-2.2; -0.3]	[-1.7; -0.4]	[-2.8; 4.5]	[-3.1; 0.2]	[-1.8; 0.1]	[-1.8; -0.6]
Change in Haematocrit[%]						
Day14-Baseline $						
- N	36	149	7	22	43	174
- Mean +/- SD	1.8 +/- 3.8	1.2 +/- 5.2	2.0 +/- 3.5	1.4 +/- 3.1	1.8 +/- 3.7	1.2 +/- 4.9
- 95% CI mean	[0.5; 3.0]	[0.4; 2.1]	[-1.2; 5.2]	[-0.0; 2.7]	[0.7; 2.9]	[0.5; 1.9]

* due to pharmacological analyses we took blood of some patients on Day2 instead of Day3
$ including data from days 12-16

No difference between G6PD sufficient and deficient patients (PCR method) can be seen regarding the group comparison of the change in haematocrit (ANOVA, tests of interaction, Hct D3-D0: p=0.50, Hct D4-D0: p=0.17, Hct D14-D0: p=0.97). There might be a slight impact on haemoglobin (ANOVA, tests of interaction, Hb D3-D0: p=0.074)

The G6PD status does not seem to have an impact on the change in haematocrit or haemoglobin within the MB+CQ group (WMW-Test, Hct D3-D0: p=0.41, Hct D4-D0: p=0.73, Hct D14-D0: p=0.84, Hb D3-D0: p=0.662)

Table 12-10: Laboratory data by WHO-Day for CQ group (FAS)

Characteristic	D0(Baseline)	D1	D2	D3	D14
Haemoglobin[g/dl]					
- N	45	4	38	1	
- Mean +/- SD	10.3+/-1.3	10.7+/-1.5	9.7+/-1.4	11.7+/-.	
- Median	10.2	10.7	9.7	11.7	
- p5, p25, p75, p95	8.3, 9.2, 11.3, 12.3	8.8, 9.6, 11.8, 12.5	7.6, 8.7, 10.8, 12.0	11.7, 11.7, 11.7, 11.7	
- Min, Max	8.0, 12.8	8.8, 12.5	7.2, 12.3	11.7, 11.7	
Haematocrit[%]					
- N	45	14	38	43	43
- Mean +/- SD	27.9+/-2.6	26.1+/-3.8	27.4+/-3.3	26.9+/-3.8	29.6+/-4.2
- Median	28.0	25.0	28.0	26.0	28.0
- p5, p25, p75, p95	24.0, 26.0, 30.0, 32.0	22.0, 22.0, 30.0, 32.0	22.0, 26.0, 30.0, 34.0	22.0, 24.0, 30.0, 32.0	24.0, 28.0, 32.0, 38.0
- Min, Max	24.0, 34.0	22.0, 32.0	20.0, 34.0	20.0, 40.0	20.0, 38.0
Creatinine[µmol/l]					
- N	45	4	38	1	
- Mean +/- SD	75.3+/-15.2	74.5+/-12.8	76.0+/-13.9	72.4+/-.	
- Median	74.4	70.1	78.5	72.4	
- p5, p25, p75, p95	52.9, 64.4, 84.1, 104.5	64.5, 67.1, 81.9, 93.2	53.1, 67.0, 85.8, 95.7	72.4, 72.4, 72.4, 72.4	
- Min, Max	44.5, 108.0	64.5, 93.2	31.6, 105.3	72.4, 72.4	
P. falciparum[/µl]					
- N	45	14	38	43	43
- Mean +/- SD	37382.2+/-45457.8	26946.4+/-76498.9	12918.4+/-19750.6	2485.3+/-8951.9	10725.6+/-27822.6
- Median	21000.0	1700.0	1750.0	100.0	0.0
- p5, p25, p75, p95	2800.0, 7000.0, 47000.0, 150000.0	200.0, 700.0, 7500.0, 290000.0	0.0, 0.0, 17000.0, 69900.0	0.0, 0.0, 1000.0, 9000.0	0.0, 0.0, 2850.0, 66000.0
- Min, Max	2500.0, 195400.0	200.0, 290000.0	0.0, 76500.0	0.0, 56700.0	0.0, 138000.0
P. ovale[/µl]					
- N	45	14	38	43	43
- Mean +/- SD	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
P. malariae[/µl]					
- N	45	14	38	43	43
- Mean +/- SD	304.4+/-1655.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	162.8+/-1067.5
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 1200.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 11000.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 7000.0

Table 12-11: Laboratory data by study day for CQ group (FAS)

Characteristic	D0(Baseline)	D1	D2	D3	D14
Haemoglobin[g/dl]					
- N	45		10	33	
- Mean +/- SD	10.3+/-1.3		9.9+/-1.3	9.9+/-1.5	
- Median	10.2		9.8	9.7	
- p5, p25, p75, p95	8.3, 9.2, 11.3, 12.3		8.1, 8.9, 10.8, 12.5	7.6, 8.7, 11.2, 12.0	
- Min, Max	8.0, 12.8		8.1, 12.5	7.2, 12.3	
Haematocrit[%]					
- N	45	43	10	33	43
- Mean +/- SD	27.9+/-2.6	26.7+/-3.2	27.4+/-3.7	27.6+/-3.3	26.9+/-3.8
- Median	28.0	26.0	28.0	28.0	26.0
- p5, p25, p75, p95	24.0, 26.0, 30.0, 32.0	22.0, 24.0, 30.0, 32.0	22.0, 24.0, 30.0, 32.0	22.0, 26.0, 30.0, 34.0	22.0, 24.0, 30.0, 32.0
- Min, Max	24.0, 34.0	22.0, 34.0	22.0, 32.0	20.0, 34.0	20.0, 40.0
Creatinine[µmol/l]					
- N	45		10	33	
- Mean +/- SD	75.3+/-15.2		67.5+/-10.9	78.2+/-13.4	
- Median	74.4		67.0	81.1	
- p5, p25, p75, p95	52.9, 64.4, 84.1, 104.5		53.1, 59.9, 70.6, 93.2	60.2, 72.4, 86.0, 95.7	
- Min, Max	44.5, 108.0		53.1, 93.2	31.6, 105.3	
P. falciparum[/µl]					
- N	45	43	10	33	43
- Mean +/- SD	37382.2+/-45457.8	19618.8+/-45312.6	11915.0+/-15638.0	11384.8+/-20063.9	2485.3+/-8951.9
- Median	21000.0	7500.0	3150.0	750.0	100.0
- p5, p25, p75, p95	2800.0, 7000.0, 47000.0, 150000.0	300.0, 1500.0, 19000.0, 52900.0	0.0, 700.0, 17000.0, 42000.0	0.0, 0.0, 13600.0, 69900.0	0.0, 0.0, 1000.0, 9000.0
- Min, Max	2500.0, 195400.0	180.0, 290000.0	0.0, 42000.0	0.0, 76500.0	0.0, 56700.0
P. ovale[/µl]					
- N	45	43	10	33	43
- Mean +/- SD	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
P. malariae[/µl]					
- N	45	43	10	33	43
- Mean +/- SD	304.4+/-1655.0	697.7+/-4575.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 1200.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 11000.0	0.0, 30000.0	0.0, 0.0	0.0, 0.0	0.0, 0.0

Table 12-12: Laboratory data by WHO-Day for CQ+MB group (FAS)

Characteristic	D0(Baseline)	D1	D2	D3	D14
Haemoglobin[g/dl]					
- N	181	11	164	5	
- Mean +/- SD	10.4+/-1.4	9.5+/-1.7	9.9+/-1.5	10.4+/-1.5	
- Median	10.2	8.7	10.0	10.8	
- p5, p25, p75, p95	8.3, 9.2, 11.4, 12.8	7.9, 8.0, 11.4, 12.4	7.5, 8.8, 10.9, 12.3	8.0, 10.0, 11.6, 11.7	
- Min, Max	8.0, 14.2	7.9, 12.4	6.4, 13.8	8.0, 11.7	
Haematocrit[%]					
- N	181	58	164	180	173
- Mean +/- SD	29.4+/-3.3	27.7+/-2.8	28.1+/-3.3	28.2+/-4.0	30.8+/-3.9
- Median	30.0	28.0	28.0	30.0	30.0
- p5, p25, p75, p95	24.0, 26.0, 32.0, 34.0	22.0, 26.0, 30.0, 32.0	22.0, 26.0, 30.0, 34.0	21.0, 26.0, 30.0, 34.0	24.0, 28.0, 32.0, 38.0
- Min, Max	22.0, 38.0	20.0, 32.0	20.0, 40.0	14.0, 36.0	20.0, 40.0
Creatinine[µmol/l]					
- N	181	11	164	5	
- Mean +/- SD	77.2+/-14.5	70.6+/-8.7	75.4+/-13.1	76.2+/-8.8	
- Median	76.4	72.1	74.3	77.3	
- p5, p25, p75, p95	57.0, 68.0, 84.8, 102.7	55.0, 63.9, 76.5, 86.9	53.4, 66.1, 85.0, 99.1	65.1, 70.9, 79.7, 88.2	
- Min, Max	37.7, 127.4	55.0, 86.9	47.0, 107.3	65.1, 88.2	
P. falciparum[/µl]					
- N	181	58	164	180	174
- Mean +/- SD	45024.9+/-64146.0	16998.8+/-34938.2	7414.6+/-23652.5	1947.4+/-8613.4	5038.8+/-16265.8
- Median	24000.0	4800.0	200.0	0.0	0.0
- p5, p25, p75, p95	3000.0, 8000.0, 55000.0, 150000.0	0.0, 1100.0, 15000.0, 100000.0	0.0, 0.0, 6375.0, 42000.0	0.0, 0.0, 500.0, 9750.0	0.0, 0.0, 1500.0, 29000.0
- Min, Max	1200.0, 508000.0	0.0, 187900.0	0.0, 260000.0	0.0, 89000.0	0.0, 115000.0
P. ovale[/µl]					
- N	181	58	164	180	174
- Mean +/- SD	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
P. malariae[/µl]					
- N	181	58	164	180	174
- Mean +/- SD	2308.8+/-17528.6	182.8+/-1378.5	8.5+/-73.8	46.7+/-596.5	804.6+/-6299.4
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 2000.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 2000.0
- Min, Max	0.0, 180000.0	0.0, 10500.0	0.0, 800.0	0.0, 8000.0	0.0, 80000.0

Table 12-13: Laboratory data by study day for CQ+MB group (FAS)

Characteristic	D0(Baseline)	D1	D2	D3	D14
Haemoglobin[g/dl]					
- N	181		40	140	
- Mean +/- SD	10.4+/-1.4		10.0+/-1.4	9.9+/-1.6	
- Median	10.2		10.2	9.9	
- p5, p25, p75, p95	8.3, 9.2, 11.4, 12.8		7.9, 8.7, 11.1, 12.0	7.5, 8.8, 10.8, 12.4	
- Min, Max	8.0, 14.2		7.3, 12.4	6.4, 13.8	
Haematocrit[%]					
- N	181	181	40	140	180
- Mean +/- SD	29.4+/-3.3	27.5+/-3.5	26.4+/-3.4	28.5+/-3.3	28.2+/-4.0
- Median	30.0	28.0	26.0	28.0	30.0
- p5, p25, p75, p95	24.0, 26.0, 32.0, 34.0	22.0, 26.0, 30.0, 34.0	20.0, 24.0, 30.0, 31.0	22.0, 26.0, 30.0, 34.0	21.0, 26.0, 30.0, 34.0
- Min, Max	22.0, 38.0	18.0, 38.0	20.0, 32.0	20.0, 40.0	14.0, 36.0
Creatinine[µmol/l]					
- N	181		40	140	
- Mean +/- SD	77.2+/-14.5		67.8+/-9.5	77.2+/-12.8	
- Median	76.4		69.1	76.0	
- p5, p25, p75, p95	57.0, 68.0, 84.8, 102.7		51.5, 63.2, 73.5, 85.4	57.2, 66.7, 86.5, 100.2	
- Min, Max	37.7, 127.4		50.0, 88.0	47.0, 107.3	
P. falciparum[/µl]					
- N	181	181	40	140	180
- Mean +/- SD	45024.9+/-64146.0	16774.8+/-31190.0	16007.8+/-42820.4	4622.0+/-11178.9	1947.4+/-8613.4
- Median	24000.0	4650.0	1350.0	100.0	0.0
- p5, p25, p75, p95	3000.0, 8000.0, 55000.0, 150000.0	100.0, 1500.0, 15400.0, 74000.0	0.0, 175.0, 9000.0, 55000.0	0.0, 0.0, 1890.0, 24800.0	0.0, 0.0, 500.0, 9750.0
- Min, Max	1200.0, 508000.0	0.0, 187900.0	0.0, 260000.0	0.0, 68600.0	0.0, 89000.0
P. ovale[/µl]					
- N	181	181	40	140	180
- Mean +/- SD	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
P. malariae[/µl]					
- N	181	181	40	140	180
- Mean +/- SD	2308.8+/-17528.6	389.0+/-4297.7	0.0+/-0.0	10.0+/-79.8	46.7+/-596.5
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 2000.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 180000.0	0.0, 56900.0	0.0, 0.0	0.0, 800.0	0.0, 8000.0

Table 12-14: Changes from baseline in laboratory data by WHO-Day for CQ group (FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
Haemoglobin[g/dl]				
- N	4	38		
- Mean +/- SD	-1.0+/-1.0	-0.3+/-1.3		
- Median	-1.0	-0.4		
- p5, p25, p75, p95	-2.0, -1.8, -0.2, 0.2	-2.5, -1.1, 0.5, 2.2		
- Min, Max	-2.0, 0.2	-3.3, 2.4		
- 95% CI mean	(-2.5; 0.6)	(-0.8; 0.1)		
- 95% CI median	(-2.0; 0.2)	(-0.9; 0.2)		
- p-Value (1)	0.2500	0.0852		
Haematocrit[%]				
- N	14	38	43	43
- Mean +/- SD	-2.0+/-3.1	-0.2+/-3.3	-0.9+/-3.1	1.8+/-3.7
- Median	-2.0	0.0	0.0	2.0
- p5, p25, p75, p95	-8.0, -4.0, 2.0, 2.0	-6.0, -2.0, 2.0, 6.0	-6.0, -2.0, 0.0, 4.0	-4.0, 0.0, 4.0, 8.0
- Min, Max	-8.0, 2.0	-8.0, 8.0	-8.0, 8.0	-6.0, 12.0
- 95% CI mean	(-3.8; -0.2)	(-1.2; 0.9)	(-1.8; 0.1)	(0.7; 2.9)
- 95% CI median	(-4.0; 2.0)	(0.0; 0.0)	(-2.0; 0.0)	(0.0; 4.0)
- p-Value (1)	0.0374	0.7862	0.0494	0.0024
Creatinine[µmol/l]				
- N	4	38		
- Mean +/- SD	-5.6+/-13.4	0.6+/-15.2		
- Median	-3.3	-0.8		
- p5, p25, p75, p95	-23.2, -15.6, 4.5, 7.5	-21.3, -11.6, 11.2, 27.9		
- Min, Max	-23.2, 7.5	-32.8, 36.2		
- 95% CI mean	(-26.8; 15.7)	(-4.3; 5.6)		
- 95% CI median	(-23.2; 7.5)	(-5.9; 5.6)		
- p-Value (1)	0.6250	0.8478		

(1) Wilcoxon Signed Rank Test

Table 12-15: Changes from baseline in laboratory data by WHO-Day for CQ group (FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
P. falciparum[/µl]				
- N	14	38	43	43
- Mean +/- SD	-18267.9+/-52769.8	-24855.3+/-36786.7	-33868.1+/-47703.2	-25627.9+/-45287.9
- Median	-17600.0	-15000.0	-16900.0	-11000.0
- p5, p25, p75, p95	-99400.0, -47100.0, -3500.0, 116000.0	-125500, -34250.0, -3100.0, 8700.0	-144100, -44150.0, -6000.0, 1600.0	-94500.0, -47000.0, -4000.0, 28400.0
- Min, Max	-99400.0, 116000.0	-138000, 29400.0	-193800, 53300.0	-173300, 71500.0
- 95% CI mean	(-48736.2; 12200.5)	(-36946.8; -12763.8)	(-48549.0; -19187.3)	(-39565.5; -11690.4)
- 95% CI median	(-47100.0; 14800.0)	(-20500.0; -6000.0)	(-34900.0; -8000.0)	(-35000.0; -5000.0)
- p-Value (1)	0.0906	<.0001	<.0001	<.0001
P. ovale[/µl]				
- N	14	38	43	43
- Mean +/- SD	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
- 95% CI mean	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- 95% CI median	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- p-Value (1)	.	.	.	.
P. malariae[/µl]				
- N	14	38	43	43
- Mean +/- SD	0.0+/-0.0	-360.5+/-1799.0	-318.6+/-1692.6	-155.8+/-2027.5
- Median	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	-1500.0, 0.0, 0.0, 0.0	-1200.0, 0.0, 0.0, 0.0	-1200.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	-11000.0, 0.0	-11000.0, 0.0	-11000.0, 7000.0
- 95% CI mean	(0.0; 0.0)	(-951.9; 230.8)	(-839.5; 202.3)	(-779.8; 468.1)
- 95% CI median	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- p-Value (1)	.	0.2500	0.2500	0.6250

(1) Wilcoxon Signed Rank Test

Table 12-16: Changes from baseline in laboratory data by study day for CQ group (FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day5-Baseline	Day14-Baseline
Haemoglobin[g/dl]					
- N		10	33		
- Mean +/- SD		-0.7+/-1.3	-0.2+/-1.3		
- Median		-0.5	-0.3		
- p5, p25, p75, p95		-3.3, -1.5, 0.2, 1.1	-2.5, -1.1, 0.5, 2.4		
- Min, Max		-3.3, 1.1	-2.5, 2.5		
- 95% CI mean		(-1.6; 0.2)	(-0.7; 0.2)		
- 95% CI median		(-2.0; 0.3)	(-0.9; 0.5)		
- p-Value (1)		0.1250	0.2186		
Haematocrit[%]					
- N	43	10	33	43	30
- Mean +/- SD	-1.2+/-3.2	-0.8+/-3.8	-0.1+/-3.0	-0.9+/-3.1	1.2+/-3.3
- Median	-2.0	0.0	0.0	0.0	2.0
- p5, p25, p75, p95	-6.0, -4.0, 2.0, 4.0	-8.0, -4.0, 2.0, 4.0	-6.0, -2.0, 0.0, 6.0	-6.0, -2.0, 0.0, 4.0	-4.0, 0.0, 4.0, 4.0
- Min, Max	-8.0, 8.0	-8.0, 4.0	-6.0, 8.0	-8.0, 8.0	-6.0, 10.0
- 95% CI mean	(-2.2; -0.2)	(-3.5; 1.9)	(-1.1; 1.0)	(-1.8; 0.1)	(-0.0; 2.4)
- 95% CI median	(-2.0; 0.0)	(-4.0; 2.0)	(0.0; 0.0)	(-2.0; 0.0)	(0.0; 2.0)
- p-Value (1)	0.0193	0.6230	0.9050	0.0494	0.0753
Creatinine[µmol/l]					
- N		10	33		
- Mean +/- SD		-0.4+/-14.3	0.4+/-15.2		
- Median		-2.4	0.8		
- p5, p25, p75, p95		-23.2, -8.0, 7.5, 27.9	-21.3, -11.6, 7.5, 22.6		
- Min, Max		-23.2, 27.9	-32.8, 36.2		
- 95% CI mean		(-10.6; 9.8)	(-5.0; 5.7)		
- 95% CI median		(-11.9; 13.7)	(-4.8; 7.1)		
- p-Value (1)		0.9219	0.8272		

(1) Wilcoxon Signed Rank Test

Table 12-17: Changes from baseline in laboratory data by study day for CQ group (FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day5-Baseline	Day14-Baseline
P. falciparum[/µl]					
- N	43	10	33	43	30
- Mean +/- SD	-16734.7+/-44074.5	-30425.0+/-41253.7	-23154.5+/-33511.0	-33868.1+/-47703.2	-25158.3+/-42921.4
- Median	-6300.0	-19650.0	-15000.0	-16900.0	-9500.0
- p5, p25, p75, p95	-97100.0, -27600.0, -1600.0, 26000.0	-138000, -40000.0, -4450.0, 2000.0	-106300, -34250.0, -4000.0, 8700.0	-144100, -44150.0, -6000.0, 1600.0	-94500.0, -48000.0, -4000.0, 28400.0
- Min, Max	-182000, 116000.0	-138000, 2000.0	-125500, 29400.0	-193800, 53300.0	-149000, 71500.0
- 95% CI mean	(-30298.8; -3170.5)	(-59936.1; -913.9)	(-35037.0; -11272.1)	(-48549.0; -19187.3)	(-41185.4; -9131.2)
- 95% CI median	(-9000.0; -2600.0)	(-47100.0; -700.0)	(-19500.0; -4600.0)	(-34900.0; -8000.0)	(-40000.0; -4800.0)
- p-Value (1)	0.0007	0.0059	<.0001	<.0001	0.0004
P. ovale[/µl]					
- N	43	10	33	43	30
- Mean +/- SD	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
- 95% CI mean	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- 95% CI median	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- p-Value (1)	.	.	.	.	.
P. malariae[/µl]					
- N	43	10	33	43	30
- Mean +/- SD	379.1+/-4924.5	0.0+/-0.0	-415.2+/-1928.4	-318.6+/-1692.6	-456.7+/-2020.9
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	-1200.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	-1500.0, 0.0, 0.0, 0.0	-1200.0, 0.0, 0.0, 0.0	-1500.0, 0.0, 0.0, 0.0
- Min, Max	-11000.0, 30000.0	0.0, 0.0	-11000.0, 0.0	-11000.0, 0.0	-11000.0, 0.0
- 95% CI mean	(-1136.5; 1894.6)	(0.0; 0.0)	(-1098.9; 268.6)	(-839.5; 202.3)	(-1211.3; 297.9)
- 95% CI median	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- p-Value (1)	0.8750	.	0.2500	0.2500	0.2500

(1) Wilcoxon Signed Rank Test

Table 12-18: Lab-Changes from baseline by WHO-Day for CQ+MB group (FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
Haemoglobin[g/dl]				
- N	11	164	5	
- Mean +/- SD	-0.7+/-1.6	-0.5+/-1.6	0.9+/-1.8	
- Median	-1.1	-0.5	0.9	
- p5, p25, p75, p95	-3.0, -1.7, 0.4, 2.5	-3.1, -1.5, 0.7, 1.8	-1.0, -0.5, 1.4, 3.6	
- Min, Max	-3.0, 2.5	-4.5, 3.8	-1.0, 3.6	
- 95% CI mean	(-1.8; 0.3)	(-0.7; -0.2)	(-1.4; 3.1)	
- 95% CI median	(-1.7; 0.6)	(-0.8; -0.2)	(-1.0; 3.6)	
- p-Value (1)	0.1475	0.0003	0.4375	
Haematocrit[%]				
- N	58	164	180	173
- Mean +/- SD	-1.9+/-3.5	-1.4+/-3.0	-1.2+/-4.0	1.4+/-3.8
- Median	-2.0	-2.0	-1.0	2.0
- p5, p25, p75, p95	-8.0, -4.0, 0.0, 4.0	-6.0, -4.0, 0.0, 4.0	-8.0, -4.0, 2.0, 4.0	-4.0, -2.0, 4.0, 8.0
- Min, Max	-10, 8.0	-12, 4.0	-14, 10.0	-8.0, 12.0
- 95% CI mean	(-2.8; -0.9)	(-1.9; -1.0)	(-1.8; -0.6)	(0.9; 2.0)
- 95% CI median	(-2.0; 0.0)	(-2.0; 0.0)	(-2.0; 0.0)	(0.0; 2.0)
- p-Value (1)	<.0001	<.0001	0.0002	<.0001
Creatinine[µmol/l]				
- N	11	164	5	
- Mean +/- SD	-3.5+/-14.0	-2.2+/-13.7	-1.9+/-12.9	
- Median	-3.7	-1.4	-2.7	
- p5, p25, p75, p95	-33.3, -7.9, 7.0, 15.5	-25.7, -11.9, 7.2, 20.3	-18.7, -9.6, 9.7, 12.0	
- Min, Max	-33.3, 15.5	-38.6, 34.6	-18.7, 12.0	
- 95% CI mean	(-12.9; 5.9)	(-4.3; -0.1)	(-17.9; 14.2)	
- 95% CI median	(-7.9; 12.1)	(-4.6; 2.6)	(-18.7; 12.0)	
- p-Value (1)	0.5771	0.0570	1.0000	

(1) Wilcoxon Signed Rank Test

Table 12-19: Lab-Changes from baseline by WHO-Day for CQ+MB group (FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
P. falciparum[/µl]				
- N	58	164	180	174
- Mean +/- SD	-34994.3+/-52454.5	-37902.5+/-63511.2	-42944.3+/-63573.3	-40137.6+/-66968.1
- Median	-20000.0	-19300.0	-21100.0	-20500.0
- p5, p25, p75, p95	-105600, -54500.0, -5500.0, 10200.0	-127000, -49000.0, -6850.0, -1800.0	-141100, -53650.0, -8000.0, -2250.0	-150000, -51000.0, -5500.0, 4200.0
- Min, Max	-320100, 28700.0	-499700, 69000.0	-507900, 18500.0	-507400, 108800.0
- 95% CI mean	(-48786.5; -21202.1)	(-47695.4; -28109.6)	(-52294.7; -33593.8)	(-50158.2; -30117.1)
- 95% CI median	(-34750.0; -13000.0)	(-22450.0; -14200.0)	(-28000.0; -17000.0)	(-26000.0; -15400.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001
P. ovale[/µl]				
- N	58	164	180	174
- Mean +/- SD	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
- 95% CI mean	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- 95% CI median	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- p-Value (1)	.	.	.	.
P. malariae[/µl]				
- N	58	164	180	174
- Mean +/- SD	-3144.8+/-23733.0	-2539.6+/-18404.7	-2275.0+/-17593.0	-1539.7+/-19034.2
- Median	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	-2000.0, 0.0, 0.0, 0.0	-2000.0, 0.0, 0.0, 0.0	-2000.0, 0.0, 0.0, 1000.0
- Min, Max	-180000, 10500.0	-180000, 800.0	-180000, 8000.0	-180000, 80000.0
- 95% CI mean	(-9385.1; 3095.5)	(-5377.5; 298.2)	(-4862.6; 312.6)	(-4387.8; 1308.5)
- 95% CI median	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- p-Value (1)	0.6250	0.0002	0.0009	0.6189

(1) Wilcoxon Signed Rank Test

Table 12-20: Lab-Changes from baseline by study day for CQ+MB group (FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day5-Baseline	Day14-Baseline
Haemoglobin[g/dl]					
- N		40	140		
- Mean +/- SD		-0.8+/-1.3	-0.4+/-1.6		
- Median		-1.0	-0.5		
- p5, p25, p75, p95		-2.6, -1.8, 0.1, 1.5	-3.2, -1.3, 0.8, 2.5		
- Min, Max		-3.0, 2.5	-4.5, 3.8		
- 95% CI mean		(-1.2; -0.4)	(-0.6; -0.1)		
- 95% CI median		(-1.4; -0.4)	(-0.7; -0.1)		
- p-Value (1)		0.0003	0.0197		
Haematocrit[%]					
- N	181	40	140	180	130
- Mean +/- SD	-1.8+/-3.1	-2.5+/-3.6	-1.0+/-3.1	-1.2+/-4.0	1.1+/-3.7
- Median	-2.0	-2.0	0.0	-1.0	2.0
- p5, p25, p75, p95	-6.0, -4.0, 0.0, 4.0	-9.0, -5.0, 0.0, 2.0	-6.0, -4.0, 0.0, 4.0	-8.0, -4.0, 2.0, 4.0	-6.0, -2.0, 4.0, 8.0
- Min, Max	-10, 8.0	-10, 8.0	-12, 8.0	-14, 10.0	-8.0, 10.0
- 95% CI mean	(-2.3; -1.4)	(-3.7; -1.3)	(-1.5; -0.5)	(-1.8; -0.6)	(0.5; 1.8)
- 95% CI median	(-2.0; -2.0)	(-4.0; -2.0)	(-2.0; 0.0)	(-2.0; 0.0)	(0.0; 2.0)
- p-Value (1)	<.0001	<.0001	0.0001	0.0002	0.0006
Creatinine[µmol/l]					
- N		40	140		
- Mean +/- SD		-1.6+/-13.3	-2.4+/-13.8		
- Median		-1.5	-1.8		
- p5, p25, p75, p95		-23.2, -11.0, 7.4, 21.4	-26.0, -11.9, 7.1, 20.0		
- Min, Max		-33.3, 23.3	-38.6, 34.6		
- 95% CI mean		(-5.8; 2.7)	(-4.7; -0.1)		
- 95% CI median		(-6.1; 6.0)	(-6.0; 2.6)		
- p-Value (1)		0.5461	0.0556		

(1) Wilcoxon Signed Rank Test

Table 12-21: Lab-Changes from baseline by study day for CQ+MB group (FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day5-Baseline	Day14-Baseline
P. falciparum[/µl]					
- N	181	40	140	180	131
- Mean +/- SD	-28250.1+/-55612.6	-47464.8+/-65576.2	-34960.9+/-60918.0	-42944.3+/-63573.3	-39405.0+/-65946.1
- Median	-13500.0	-29300.0	-17300.0	-21100.0	-20000.0
- p5, p25, p75, p95	-119800, -39000.0, -3600.0, 21700.0	-152550, -61550.0, -15400.0, 1400.0	-127500, -44600.0, -6000.0, -2000.0	-141100, -53650.0, -8000.0, -2250.0	-133000, -50700.0, -5400.0, 4000.0
- Min, Max	-358600, 84000.0	-353300, 69000.0	-499700, 64300.0	-507900, 18500.0	-507400, 108800.0
- 95% CI mean	(-36406.7; -20093.4)	(-68437.0; -26492.5)	(-45140.4; -24781.3)	(-52294.7; -33593.8)	(-50803.9; -28006.1)
- 95% CI median	(-18000.0; -9300.0)	(-50960.0; -18800.0)	(-21000.0; -12100.0)	(-28000.0; -17000.0)	(-28000.0; -13600.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001
P. ovale[/µl]					
- N	181	40	140	180	131
- Mean +/- SD	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0	0.0+/-0.0
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0
- Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
- 95% CI mean	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- 95% CI median	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- p-Value (1)	.	.	.	.	.
P. malariae[/µl]					
- N	181	40	140	180	131
- Mean +/- SD	-1919.9+/-15241.6	0.0+/-0.0	-2975.0+/-19897.6	-2275.0+/-17593.0	-806.1+/-15252.6
- Median	0.0	0.0	0.0	0.0	0.0
- p5, p25, p75, p95	-2000.0, 0.0, 0.0, 0.0	0.0, 0.0, 0.0, 0.0	-5100.0, 0.0, 0.0, 0.0	-2000.0, 0.0, 0.0, 0.0	-1800.0, 0.0, 0.0, 800.0
- Min, Max	-180000, 10500.0	0.0, 0.0	-180000, 800.0	-180000, 8000.0	-150000, 80000.0
- 95% CI mean	(-4155.4; 315.6)	(0.0; 0.0)	(-6299.9; 349.9)	(-4862.6; 312.6)	(-3442.5; 1830.3)
- 95% CI median	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
- p-Value (1)	0.0024	.	0.0002	0.0009	0.6776

(1) Wilcoxon Signed Rank Test

Table 12-22: Feverflow by WHO-Day for CQ group (FAS)

Characteristic	D0	D1	D2	D3	D14
min fever per day					
- N	43	43	43	43	43
- Mean +/- SD	36.9+/- 0.6	37.0+/- 0.7	36.7+/- 0.6	36.6+/- 0.6	37.4+/- 0.6
- Median	36.9	37.0	36.5	36.6	37.4
- p5, p25, p75, p95	36.0, 36.4, 37.3, 38.2	36.0, 36.5, 37.4, 37.9	36.0, 36.2, 37.0, 37.4	36.0, 36.3, 36.8, 37.7	36.5, 37.1, 37.6, 38.4
- Min, Max	35.8, 38.5	35.7, 39.2	36.0, 39.0	35.7, 38.4	36.4, 39.7
mean fever per day					
- N	43	43	43	43	43
- Mean +/- SD	37.8+/- 0.7	37.7+/- 0.7	37.3+/- 0.5	37.1+/- 0.6	37.4+/- 0.6
- Median	37.8	37.6	37.1	37.0	37.4
- p5, p25, p75, p95	37.0, 37.3, 38.3, 39.0	36.9, 37.2, 38.3, 39.1	36.7, 37.0, 37.6, 38.6	36.6, 36.7, 37.2, 38.3	36.5, 37.1, 37.6, 38.4
- Min, Max	36.7, 39.4	36.8, 39.5	36.7, 39.4	36.0, 39.3	36.4, 39.7
max fever per day					
- N	43	43	43	43	43
- Mean +/- SD	38.8+/- 1.0	38.6+/- 1.0	38.0+/- 0.7	37.7+/- 0.8	37.4+/- 0.6
- Median	38.8	38.4	37.9	37.5	37.4
- p5, p25, p75, p95	37.4, 37.9, 39.6, 40.3	37.3, 37.7, 39.5, 40.3	37.3, 37.6, 38.3, 39.6	36.8, 37.2, 38.0, 39.2	36.5, 37.1, 37.6, 38.4
- Min, Max	37.2, 40.3	37.1, 40.5	37.2, 40.6	36.0, 40.3	36.4, 39.7

min fever means the minimum of all fever measurements per day of one patient; max, mean respectively

Table 12-23: Feverflow by WHO-Day for CQ+MB group (FAS)

Characteristic	D0	D1	D2	D3	D14
min fever per day					
- N	181	181	181	180	173
- Mean +/- SD	37.1+/- 0.7	36.9+/- 0.7	36.6+/- 0.7	36.7+/- 0.7	37.4+/- 0.6
- Median	37.0	36.7	36.5	36.6	37.3
- p5, p25, p75, p95	36.0, 36.7, 37.4, 38.3	36.0, 36.4, 37.2, 38.2	36.0, 36.2, 37.0, 37.9	36.0, 36.2, 37.0, 37.9	36.6, 37.0, 37.7, 38.7
- Min, Max	35.7, 39.1	35.5, 39.3	35.4, 39.7	35.5, 39.8	36.3, 40.2
mean fever per day					
- N	181	181	181	180	173
- Mean +/- SD	37.9+/- 0.8	37.6+/- 0.8	37.3+/- 0.7	37.2+/- 0.7	37.4+/- 0.6
- Median	37.8	37.4	37.1	37.1	37.3
- p5, p25, p75, p95	36.9, 37.3, 38.4, 39.2	36.6, 37.1, 38.1, 39.1	36.6, 36.8, 37.6, 38.7	36.5, 36.8, 37.4, 38.5	36.6, 37.0, 37.7, 38.7
- Min, Max	36.5, 39.9	36.1, 39.8	36.4, 40.8	35.8, 40.5	36.3, 40.2
max fever per day					
- N	181	181	181	180	173
- Mean +/- SD	38.8+/- 1.0	38.5+/- 1.0	37.9+/- 0.8	37.7+/- 0.9	37.4+/- 0.6
- Median	38.6	38.3	37.7	37.5	37.3
- p5, p25, p75, p95	37.3, 37.9, 39.5, 40.5	37.1, 37.6, 39.3, 40.2	37.0, 37.3, 38.3, 39.7	36.7, 37.2, 37.9, 39.8	36.6, 37.0, 37.7, 38.7
- Min, Max	37.0, 41.4	36.2, 41.0	36.7, 41.3	35.8, 41.4	36.3, 40.2

min fever means the minimum of all fever measurements per day of one patient; max, mean respectively

Table 12-24: Feverflow by study day for CQ group (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14
min fever per day						
- N	43	43	43	43	43	43
- Mean +/- SD	38.3+/- 0.9	36.9+/- 0.6	36.8+/- 0.5	36.7+/- 0.6	36.7+/- 0.6	37.4+/- 0.6
- Median	38.0	36.9	36.8	36.5	36.6	37.4
- p5, p25, p75, p95	37.1, 37.7, 38.8, 40.0	36.0, 36.4, 37.2, 37.9	36.0, 36.5, 37.1, 37.7	36.0, 36.2, 37.0, 37.4	36.0, 36.3, 36.8, 37.7	36.5, 37.1, 37.6, 38.4
- Min, Max	36.8, 40.2	35.8, 38.3	35.7, 38.0	36.0, 39.0	35.7, 38.6	36.4, 39.7
mean fever per day						
- N	43	43	43	43	43	43
- Mean +/- SD	38.3+/- 0.9	37.8+/- 0.7	37.6+/- 0.6	37.3+/- 0.5	37.0+/- 0.7	37.4+/- 0.6
- Median	38.0	37.9	37.5	37.2	36.9	37.4
- p5, p25, p75, p95	37.1, 37.7, 38.8, 40.0	36.8, 37.2, 38.3, 38.8	37.0, 37.1, 38.2, 38.8	36.8, 37.0, 37.5, 38.2	36.4, 36.6, 37.2, 38.5	36.5, 37.1, 37.6, 38.4
- Min, Max	36.8, 40.2	36.6, 39.3	36.8, 38.9	36.5, 39.3	36.0, 39.5	36.4, 39.7
max fever per day						
- N	43	43	43	43	43	43
- Mean +/- SD	38.3+/- 0.9	38.8+/- 1.0	38.5+/- 1.0	38.0+/- 0.5	37.4+/- 0.8	37.4+/- 0.6
- Median	38.0	39.0	38.1	37.9	37.2	37.4
- p5, p25, p75, p95	37.1, 37.7, 38.8, 40.0	37.3, 37.8, 39.6, 40.3	37.4, 37.7, 39.2, 40.4	37.3, 37.6, 38.2, 39.0	36.4, 37.0, 37.7, 38.9	36.5, 37.1, 37.6, 38.4
- Min, Max	36.8, 40.2	36.8, 40.3	37.3, 40.6	37.0, 39.9	36.0, 40.3	36.4, 39.7

min fever means the minimum of all fever measurements per day of one patient; max, mean respectively

Table 12-25: Feverflow by study day for CQ+MB group (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14
min fever per day						
- N	177	181	181	180	180	173
- Mean +/- SD	38.2+/- 1.1	37.0+/- 0.7	36.8+/- 0.7	36.6+/- 0.7	36.7+/- 0.7	37.4+/- 0.6
- Median	38.2	37.0	36.7	36.5	36.6	37.3
- p5, p25, p75, p95	36.7, 37.5, 39.0, 40.0	36.0, 36.6, 37.4, 38.4	36.0, 36.4, 37.2, 38.1	36.0, 36.2, 36.9, 37.9	36.0, 36.3, 37.0, 38.1	36.6, 37.0, 37.7, 38.7
- Min, Max	35.7, 40.8	35.8, 39.3	35.5, 39.3	35.4, 39.2	35.5, 40.0	36.3, 40.2
mean fever per day						
- N	177	181	181	180	180	173
- Mean +/- SD	38.2+/- 1.0	37.9+/- 0.7	37.5+/- 0.8	37.3+/- 0.7	37.1+/- 0.7	37.4+/- 0.6
- Median	38.2	37.8	37.3	37.1	37.0	37.3
- p5, p25, p75, p95	36.7, 37.5, 39.0, 40.0	37.0, 37.3, 38.4, 39.3	36.6, 36.9, 38.0, 39.0	36.6, 36.8, 37.5, 38.8	36.2, 36.6, 37.3, 38.4	36.6, 37.0, 37.7, 38.7
- Min, Max	35.7, 40.8	36.7, 39.8	36.1, 40.0	36.2, 39.8	35.8, 40.4	36.3, 40.2
max fever per day						
- N	177	181	181	180	180	173
- Mean +/- SD	38.2+/- 1.0	38.8+/- 1.0	38.2+/- 1.0	37.9+/- 0.8	37.6+/- 0.9	37.4+/- 0.6
- Median	38.2	38.6	37.9	37.7	37.4	37.3
- p5, p25, p75, p95	36.7, 37.5, 39.0, 40.0	37.3, 37.9, 39.5, 40.4	37.1, 37.4, 38.8, 40.2	37.0, 37.3, 38.2, 39.8	36.5, 37.0, 37.8, 39.7	36.6, 37.0, 37.7, 38.7
- Min, Max	35.7, 40.8	37.0, 41.4	36.5, 41.3	36.5, 41.4	35.8, 40.8	36.3, 40.2

min fever means the minimum of all fever measurements per day of one patient; max, mean respectively

Table 12-26: Concomitant medication by generic name and group (FAS)

Medication group - generic name	CQ (N=120)	CQ+MB (N=469)
Antibiotic	33(27.5%)	158(33.7%)
- Amoxicillin	3(9.1%)	28(17.7%)
- Cebemyxine	0(0.0%)	1(0.6%)
- Cefadroxil	2(6.1%)	10(6.3%)
- Ceftriaxon	0(0.0%)	2(1.3%)
- Ciprofloxacin	0(0.0%)	2(1.3%)
- Cotrimoxazol	9(27.3%)	32(20.3%)
- Erythromycin	12(36.4%)	64(40.5%)
- Gentamycin	0(0.0%)	2(1.3%)
- Metronidazol	7(21.2%)	17(10.8%)
Antihistaminic	5(4.2%)	6(1.3%)
- Chlorpheniramine	2(40.0%)	2(33.3%)
- Mequitazin	3(60.0%)	4(66.7%)
Antimalarial (1)	30(25.0%)	106(22.6%)
- Quinine	5(16.7%)	10(9.4%)
- Sulfadoxa/Pyrimethamin	25(83.3%)	96(90.6%)
Antipyretic	37(30.8%)	138(29.4%)
- Ibuprofen	3(8.1%)	3(2.2%)
- Paracetamol	34(91.9%)	135(97.8%)
Others	15(12.5%)	61(13.0%)
- Albendazol	7(46.7%)	7(11.5%)
- Carbocystein	2(13.3%)	15(24.6%)
- Glucose/Electrolyte Solution	2(13.3%)	16(26.2%)
- Metopimazin	3(20.0%)	20(32.8%)
- Trimebutine	1(6.7%)	3(4.9%)

(1) apart from CQ or MB

Table 12-27: Primary analysis for G6PD def. children (FAS)

Characteristic	CQ (N=6)	CQ+MB (N=24)	Comparison (N=30)
Haemolysis			
- Yes	0(0.0%)	0(0.0%)	
- No	6(100.0%)	24(100.0%)	
SAE			
- Yes	0(0.0%)	0(0.0%)	
- No	6(100.0%)	24(100.0%)	
Changes in HB[g/dl] (3)			
- N	5	21	
- Mean +/- SD	0.4+/- 1.2	-0.7+/- 1.5	1.1+/- 1.4
- Median	0.1	-0.6	
- Min, Max	-0.6, 2.4	-4.1, 2.9	
- p5, p25, p75, p95	-0.6, -0.4, 0.4, 2.4	-2.7, -1.1, -0.1, 1.1	
- 95% CI mean			[-0.4; 2.5]
- p-Value (4)			0.1256
Changes in HCT[%] (5)			
- N	6	24	
- Mean +/- SD	1.3+/- 4.1	-1.4+/- 3.9	2.8+/- 3.9
- Median	0.0	-1.0	
- Min, Max	-4.0, 8.0	-10, 4.0	
- p5, p25, p75, p95	-4.0, 0.0, 4.0, 8.0	-8.0, -4.0, 2.0, 4.0	
- 95% CI mean			[-0.9; 6.4]
- p-Value (4)			0.2586

(1) CI=95% confidence interval of the relative risk of SAE rates
(2) Chi-Square-test for differences of incidence rates
(3) change D2(WHO)-Baseline
(4) U-Test = WMW-Test
(5) change D3(WHO)-Baseline

Table 12-28: Primary analysis for G6PD def. children by WHO Day (PP)

Characteristic	CQ (N=6)	CQ+MB (N=22)	Comparison (N=28)
Haemolysis			
- Yes	0(0.0%)	0(0.0%)	
- No	6(100.0%)	22(100.0%)	
SAE			
- Yes	0(0.0%)	0(0.0%)	
- No	6(100.0%)	22(100.0%)	
Changes in HB[g/dl] (3)			
- N	5	19	
- Mean +/- SD	0.4+/- 1.2	-0.5+/- 1.3	0.9+/- 1.3
- Median	0.1	-0.5	
- Min, Max	-0.6, 2.4	-2.7, 2.9	
- p5, p25, p75, p95	-0.6, -0.4, 0.4, 2.4	-2.7, -1.1, 0.5, 2.9	
- 95% CI mean			[-0.5; 2.2]
- p-Value (4)			0.1762
Changes in HCT[%] (5)			
- N	6	22	
- Mean +/- SD	1.3+/- 4.1	-1.2+/- 4.0	2.5+/- 4.0
- Median	0.0	0.0	
- Min, Max	-4.0, 8.0	-10, 4.0	
- p5, p25, p75, p95	-4.0, 0.0, 4.0, 8.0	-8.0, -4.0, 2.0, 4.0	
- 95% CI mean			[-1.3; 6.3]
- p-Value (4)			0.3482

(1) CI=95% confidence interval of the relative risk of SAE rates
(2) Chi-Square-test for differences of incidence rates
(3) change D2(WHO)-Baseline
(4) U-Test = WMW-Test
(5) change D3(WHO)-Baseline

Table 12-29: Primary analysis for G6PD def. children (FAS)

Characteristic	CQ (N=6)	CQ+MB (N=24)	Comparison (N=30)
Haemolysis			
- Yes	0(0.0%)	0(0.0%)	
- No	6(100.0%)	24(100.0%)	
SAE			
- Yes	0(0.0%)	0(0.0%)	
- No	6(100.0%)	24(100.0%)	
Changes in HB[g/dl] (3)			
- N	5	20	
- Mean +/- SD	1.0+/- 1.4	-0.6+/- 1.4	1.5+/- 1.4
- Median	0.4	-0.5	
- Min, Max	-0.6, 2.5	-4.1, 2.9	
- p5, p25, p75, p95	-0.6, 0.1, 2.4, 2.5	-3.2, -1.1, 0.2, 2.0	
- 95% CI mean			[0.0; 3.0]
- p-Value (4)			0.071
Changes in HCT[%] (5)			
- N	6	24	
- Mean +/- SD	1.3+/- 4.1	-1.4+/- 3.9	2.8+/- 3.9
- Median	0.0	-1.0	
- Min, Max	-4.0, 8.0	-10, 4.0	
- p5, p25, p75, p95	-4.0, 0.0, 4.0, 8.0	-8.0, -4.0, 2.0, 4.0	
- 95% CI mean			[-0.9; 6.4]
- p-Value (4)			0.259

(1) CI=95% confidence interval of the relative risk of SAE rates
(2) Chi-Square-test for differences of incidence rates
(3) change Day4(Study day)-Baseline
(4) U-Test = WMW-Test
(5) change Day5(Study day)-Baseline

Table 12-30: Primary analysis for G6PD def. children by study day (PP)

Characteristic	CQ (N=6)	CQ+MB (N=22)	Comparison (N=28)
Haemolysis			
- Yes	0(0.0%)	0(0.0%)	
- No	6(100.0%)	22(100.0%)	
SAE			
- Yes	0(0.0%)	0(0.0%)	
- No	6(100.0%)	22(100.0%)	
Changes in HB[g/dl] (3)			
- N	5	18	
- Mean +/- SD	1.0+/- 1.4	-0.4+/- 1.2	1.3+/- 1.3
- Median	0.4	-0.5	
- Min, Max	-0.6, 2.5	-2.2, 2.9	
- p5, p25, p75, p95	-0.6, 0.1, 2.4, 2.5	-2.2, -1.1, 0.5, 2.9	
- 95% CI mean			[-0.0; 2.7]
- p-Value (4)			0.101
Changes in HCT[%] (5)			
- N	6	22	
- Mean +/- SD	1.3+/- 4.1	-1.2+/- 4.0	2.5+/- 4.0
- Median	0.0	0.0	
- Min, Max	-4.0, 8.0	-10, 4.0	
- p5, p25, p75, p95	-4.0, 0.0, 4.0, 8.0	-8.0, -4.0, 2.0, 4.0	
- 95% CI mean			[-1.3; 6.3]
- p-Value (4)			0.348

(1) CI=95% confidence interval of the relative risk of SAE rates
(2) Chi-Square-test for differences of incidence rates
(3) change Day4(Study day)-Baseline
(4) U-Test = WMW-Test
(5) change Day5(Study day)-Baseline

Table 12-31: Treatment failure by group (FAS)

	CQ (N=45)	CQ+MB (N=181)	Total (N=226)
ETF	17(37.8%)	55(30.4%)	72(31.9%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	2(11.8%)	1(1.8%)	3(4.2%)
- reason3	7(41.2%)	40(72.7%)	47(65.3%)
- reason2+4	1(5.9%)	1(1.8%)	2(2.8%)
- reason2+3	2(11.8%)	1(1.8%)	3(4.2%)
- reason2+3+4	1(5.9%)	3(5.5%)	4(5.6%)
- reason3+4	1(5.9%)	7(12.7%)	8(11.1%)
- reason4	1(5.9%)	1(1.8%)	2(2.8%)
- reason5	2(11.8%)	1(1.8%)	3(4.2%)
95% CI (1)			[0.36; 1.42]
p-Value (2)			0.439
LCF	9(20.0%)	33(18.2%)	42(18.6%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	7(77.8%)	22(66.7%)	29(69.0%)
- reason3	0(0.0%)	4(12.1%)	4(9.5%)
- reason4	2(22.2%)	7(21.2%)	9(21.4%)
95% CI (1)			[0.39; 2.03]
p-Value (2)			0.953
TF	26(57.8%)	88(48.6%)	114(50.4%)
- ETF	17(65.4%)	55(62.5%)	72(63.2%)
- LCF	9(34.6%)	33(37.5%)	42(36.8%)
95% CI (1)			[0.36; 1.34]
p-Value (2)			0.351
LPF	5(11.1%)	21(11.6%)	26(11.5%)
- reason1	5(100.0%)	21(100.0%)	26(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
95% CI (1)			[0.37; 2.96]

percentages of ETF, LTF and TF are based on the number of pat. by group, otherwise (for subreasons) based on the number of failures.

ETF-reason1: Severe malaria on D1-D3(WHO); reason2: Parasitaemia on D2(WHO)> baseline count

ETF-reason3: Fever(>=37,5°C)on D3(WHO) and parasitaemia > 0; reason4: Parasitaemia on D3(WHO)>= 25% of baseline count

ETF-reason5: Missing information

LTF-reason1: Severe malaria on D4-D14(WHO); reason2: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LTF-reason3: Missing Information

LTF-reason4: treated (D4-D13) with antimalarials although no fever and/or no parasites

LPF-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

(1) CI = confidence interval for the odds ratio

Table 12-32: Treatment failure by group (PP)

	CQ (N=41)	CQ+MB (N=166)	Total (N=207)
ETF	15(36.6%)	48(28.9%)	63(30.4%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	2(13.3%)	0(0.0%)	2(3.2%)
- reason3	7(46.7%)	36(75.0%)	43(68.3%)
- reason2+4	1(6.7%)	1(2.1%)	2(3.2%)
- reason2+3	2(13.3%)	1(2.1%)	3(4.8%)
- reason2+3+4	1(6.7%)	3(6.3%)	4(6.3%)
- reason3+4	1(6.7%)	6(12.5%)	7(11.1%)
- reason4	1(6.7%)	1(2.1%)	2(3.2%)
- reason5	0(0.0%)	0(0.0%)	0(0.0%)
95% CI (1)			[0.34; 1.45]
p-Value (2)			0.444
LCF	7(17.1%)	25(15.1%)	32(15.5%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	7(100.0%)	22(100.0%)	29(100.0%)
- reason3	0(0.0%)	0(0.0%)	0(0.0%)
95% CI (1)			[0.34; 2.16]
p-Value (2)			0.938
TF	22(53.7%)	73(44.0%)	95(45.9%)
- ETF	15(68.2%)	48(65.8%)	63(66.3%)
- LCF	7(31.8%)	25(34.2%)	32(33.7%)
95% CI (1)			[0.34; 1.35]
p-Value (2)			0.348
LPF	5(12.2%)	21(12.7%)	26(12.6%)
- reason1	5(100.0%)	21(100.0%)	26(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
95% CI (1)			[0.37; 2.95]
p-Value (2)			1.000

percentages of ETF, LTF and TF are based on the number of pat. by group, otherwise (for subreasons) based on the number of failures.

ETF-reason1: Severe malaria on D1-D3(WHO); reason2: Parasitaemia on D2(WHO)> baseline count

ETF-reason3: Fever(>=37,5°C)on D3(WHO) and parasitaemia > 0; reason4: Parasitaemia on D3(WHO)>= 25% of baseline count

ETF-reason5: Missing information

LTF-reason1: Severe malaria on D4-D14(WHO); reason2: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LTF-reason3: Missing Information

LPF-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

(1) CI = confidence interval for the odds ratio

(2) Continuity Adj. Chi-Square

Table 12-33: Treatment failure by group for children < 2 years(FAS)

	CQ (N=13)	CQ+MB (N=61)	Total (N=74)
ETF	6(46.2%)	26(42.6%)	32(43.2%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	1(3.8%)	1(3.1%)
- reason3	2(33.3%)	17(65.4%)	19(59.4%)
- reason2+4	0(0.0%)	1(3.8%)	1(3.1%)
- reason2+3	2(33.3%)	1(3.8%)	3(9.4%)
- reason2+3+4	1(16.7%)	0(0.0%)	1(3.1%)
- reason3+4	0(0.0%)	5(19.2%)	5(15.6%)
- reason4	0(0.0%)	0(0.0%)	0(0.0%)
- reason5	1(16.7%)	1(3.8%)	2(6.3%)
95% CI (1)			[0.26; 2.89]
p-Value (2)			1.000
LCF	2(15.4%)	9(14.8%)	11(14.9%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	1(50.0%)	5(55.6%)	6(54.5%)
- reason3	0(0.0%)	1(11.1%)	1(9.1%)
- reason4	1(50.0%)	3(33.3%)	4(36.4%)
95% CI (1)			[0.18; 5.03]
p-Value (2)			1.000
TF	8(61.5%)	35(57.4%)	43(58.1%)
- ETF	6(75.0%)	26(74.3%)	32(74.4%)
- LCF	2(25.0%)	9(25.7%)	11(25.6%)
95% CI (1)			[0.25; 2.87]
p-Value (2)			1.000
LPF	1(7.7%)	3(4.9%)	4(5.4%)
- reason1	1(100.0%)	3(100.0%)	4(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
95% CI (1)			[0.06; 6.49]

percentages of ETF, LTF and TF are based on the number of pat. by group, otherwise (for subreasons) based on the number of failures.

ETF-reason1: Severe malaria on D1-D3(WHO); reason2: Parasitaemia on D2(WHO)> baseline count

ETF-reason3: Fever(>=37,5°C)on D3(WHO) and parasitaemia > 0; reason4: Parasitaemia on D3(WHO)>= 25% of baseline count

ETF-reason5: Missing information

LTF-reason1: Severe malaria on D4-D14(WHO); reason2: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LTF-reason3: Missing Information

LTF-reason4: treated (D4-D13) with antimalarials although no fever and/or no parasites

LPF-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

(1) CI = confidence interval for the odds ratio

(2) Continuity Adj. Chi-Square

Table 12-34: Treatment failure by group for children >= 2 years(FAS)

	CQ (N=32)	CQ+MB (N=120)	Total (N=152)
ETF	11(34.4%)	29(24.2%)	40(26.3%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	2(18.2%)	0(0.0%)	2(5.0%)
- reason3	5(45.5%)	23(79.3%)	28(70.0%)
- reason2+4	1(9.1%)	0(0.0%)	1(2.5%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3+4	0(0.0%)	3(10.3%)	3(7.5%)
- reason3+4	1(9.1%)	2(6.9%)	3(7.5%)
- reason4	1(9.1%)	1(3.4%)	2(5.0%)
- reason5	1(9.1%)	0(0.0%)	1(2.5%)
95% CI (1)			[0.26; 1.41]
p-Value (2)			0.348
LCF	7(21.9%)	24(20.0%)	31(20.4%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	6(85.7%)	17(70.8%)	23(74.2%)
- reason3	0(0.0%)	3(12.5%)	3(9.7%)
- reason4	1(14.3%)	4(16.7%)	5(16.1%)
95% CI (1)			[0.35; 2.31]
p-Value (2)			1.000
TF	18(56.3%)	53(44.2%)	71(46.7%)
- ETF	11(61.1%)	29(54.7%)	40(56.3%)
- LCF	7(38.9%)	24(45.3%)	31(43.7%)
95% CI (1)			[0.28; 1.35]
p-Value (2)			0.309
LPF	4(12.5%)	18(15.0%)	22(14.5%)
- reason1	4(100.0%)	18(100.0%)	22(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
95% CI (1)			[0.39; 3.95]

percentages of ETF, LTF and TF are based on the number of pat. by group, otherwise (for subreasons) based on the number of failures.

ETF-reason1: Severe malaria on D1-D3(WHO); reason2: Parasitaemia on D2(WHO)> baseline count

ETF-reason3: Fever(>=37,5°C)on D3(WHO) and parasitaemia > 0; reason4: Parasitaemia on D3(WHO)>= 25% of baseline count

ETF-reason5: Missing information

LTF-reason1: Severe malaria on D4-D14(WHO); reason2: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LTF-reason3: Missing Information

LTF-reason4: treated (D4-D13) with antimalarials although no fever and/or no parasites

LPF-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

(1) CI = confidence interval for the odds ratio

(2) Continuity Adj. Chi-Square

Table 12-35: Treatment failure by group for children from Nouna town (FAS)

	CQ (N=34)	CQ+MB (N=139)	Total (N=173)
ETF	17(50.0%)	53(38.1%)	70(40.5%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	2(11.8%)	1(1.9%)	3(4.3%)
- reason3	7(41.2%)	38(71.7%)	45(64.3%)
- reason2+4	1(5.9%)	1(1.9%)	2(2.9%)
- reason2+3	2(11.8%)	1(1.9%)	3(4.3%)
- reason2+3+4	1(5.9%)	3(5.7%)	4(5.7%)
- reason3+4	1(5.9%)	7(13.2%)	8(11.4%)
- reason4	1(5.9%)	1(1.9%)	2(2.9%)
- reason5	2(11.8%)	1(1.9%)	3(4.3%)
95% CI (1)			[0.29; 1.31]
p-Value (2)			0.285
LCF	5(14.7%)	29(20.9%)	34(19.7%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	5(100.0%)	19(65.5%)	24(70.6%)
- reason3	0(0.0%)	4(13.8%)	4(11.8%)
- reason4	0(0.0%)	6(20.7%)	6(17.6%)
95% CI (1)			[0.54; 4.30]
p-Value (2)			0.569
TF	22(64.7%)	82(59.0%)	104(60.1%)
- ETF	17(77.3%)	53(64.6%)	70(67.3%)
- LCF	5(22.7%)	29(35.4%)	34(32.7%)
95% CI (1)			[0.36; 1.71]
p-Value (2)			0.679
LPF	3(8.8%)	15(10.8%)	18(10.4%)
- reason1	3(100.0%)	15(100.0%)	18(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
95% CI (1)			[0.34; 4.59]

percentages of ETF, LTF and TF are based on the number of pat. by group, otherwise (for subreasons) based on the number of failures.

ETF-reason1: Severe malaria on D1-D3(WHO); reason2: Parasitaemia on D2(WHO)> baseline count

ETF-reason3: Fever(>=37,5°C)on D3(WHO) and parasitaemia > 0; reason4: Parasitaemia on D3(WHO)>= 25% of baseline count

ETF-reason5: Missing information

LTF-reason1: Severe malaria on D4-D14(WHO); reason2: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LTF-reason3: Missing Information

LTF-reason4: treated (D4-D13) with antimalarials although no fever and/or no parasites

LPF-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

(1) CI = confidence interval for the odds ratio

(2) Continuity Adj. Chi-Square

Table 12-36: Treatment failure by group for children from villages (FAS)

	CQ (N=11)	CQ+MB (N=42)	Total (N=53)
ETF	0(0.0%)	2(4.8%)	2(3.8%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	0(0.0%)	2(100.0%)	2(100.0%)
- reason2+4	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3+4	0(0.0%)	0(0.0%)	0(0.0%)
- reason3+4	0(0.0%)	0(0.0%)	0(0.0%)
- reason4	0(0.0%)	0(0.0%)	0(0.0%)
- reason5	0(0.0%)	0(0.0%)	0(0.0%)
p-Value (2)			1.000
LCF	4(36.4%)	4(9.5%)	8(15.1%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	2(50.0%)	3(75.0%)	5(62.5%)
- reason3	0(0.0%)	0(0.0%)	0(0.0%)
- reason4	2(50.0%)	1(25.0%)	3(37.5%)
95% CI (1)			[0.04; 0.92]
p-Value (2)			0.082
TF	4(36.4%)	6(14.3%)	10(18.9%)
- ETF	0(0.0%)	2(33.3%)	2(20.0%)
- LCF	4(100.0%)	4(66.7%)	8(80.0%)
95% CI (1)			[0.06; 1.31]
p-Value (2)			0.218
LPF	2(18.2%)	6(14.3%)	8(15.1%)
- reason1	2(100.0%)	6(100.0%)	8(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
95% CI (1)			[0.13; 4.36]

percentages of ETF, LTF and TF are based on the number of pat. by group, otherwise (for subreasons) based on the number of failures.

ETF-reason1: Severe malaria on D1-D3(WHO); reason2: Parasitaemia on D2(WHO)> baseline count

ETF-reason3: Fever(>=37,5°C)on D3(WHO) and parasitaemia > 0; reason4: Parasitaemia on D3(WHO)>= 25% of baseline count

ETF-reason5: Missing information

LTF-reason1: Severe malaria on D4-D14(WHO); reason2: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LTF-reason3: Missing Information

LTF-reason4: treated (D4-D13) with antimalarials although no fever and/or no parasites

LPF-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

(1) CI = confidence interval for the odds ratio

(2) Continuity Adj. Chi-Square

Table 12-37: Clearance time by group (FAS)

	CQ (N=45)	CQ+MB (N=181)	Comparison
Fever clearance time[hour]			
- N	43	181	
- Median	7.3	9.0	
- Min, Max	0.3, 90.7	0.1, 92.0	
- p-value: log-rank-test			0.224
- p-value: wilcoxon-test			0.347
Pat. < 37.5°C for at least one time	42(97.7%)	173(95.6%)	
Pat. > 37.5°C at all times	1(2.3%)	8(4.4%)	
- at least one fever measurement on D3	1(100.0%)	8(100.0%)	
- no fever measurement on D3	0(0.0%)	0(0.0%)	
P.falciparum clearance time[hour]			
- N	43	181	
- Median	87.3	86.8	
- Min, Max	50.6, 91.3	22.8, 91.1	
- p-value: log-rank-test			0.195
- p-value: wilcoxon-test			0.274
Pat. parasitaemia is not detectable	21(48.8%)	105(58.0%)	
Pat. parasitaemia is detectable at all times	22(51.2%)	76(42.0%)	
- blood sample available on D3	22(100.0%)	75(98.7%)	
- no blood sample on D3	0(0.0%)	1(1.3%)	

Table 12-38: Clearance time by group (PP)

	CQ (N=41)	CQ+MB (N=166)	Comparison
Fever clearance time[hour]			
- N	41	166	
- Median	8.0	8.8	
- Min, Max	0.3, 90.7	0.1, 92.0	
- p-value: log-rank-test			0.435
- p-value: wilcoxon-test			0.725
Pat. < 37.5°C for at least one time	40(97.6%)	159(95.8%)	
Pat. > 37.5°C at all times	1(2.4%)	7(4.2%)	
- at least one fever measurement on D3	1(100.0%)	7(100.0%)	
- no fever measurement on D3	0(0.0%)	0(0.0%)	
P.falciparum clearance time[hour]			
- N	41	166	
- Median	91.3	86.4	
- Min, Max	50.6, 91.3	22.8, 91.1	
- p-value: log-rank-test			0.102
- p-value: wilcoxon-test			0.140
Pat. parasitaemia is not detectable	19(46.3%)	98(59.0%)	
Pat. parasitaemia is detectable at all times	22(53.7%)	68(41.0%)	
- blood sample available on D3	22(100.0%)	68(100.0%)	
- no blood sample on D3	0(0.0%)	0(0.0%)	

Table 12-39: Acceptance of MB (FAS)

	CQ+MB (N=181)
Acceptance	
- well	94(53.1%)
- moderate	83(46.9%)
- bad	0(0.0%)

4 missings

Table 12-40: End of study by group (FAS)

	CQ (N=45)	CQ+MB (N=181)	Total (N=226)
FAS population			
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	0(0.0%)	0(0.0%)	0(0.0%)
- reason4	2(4.4%)	1(0.6%)	3(1.3%)
- reason5	0(0.0%)	0(0.0%)	0(0.0%)
not withdrawn until D3	43(95.6%)	180(99.4%)	223(98.7%)
- no data on D14	2(4.4%)	7(3.9%)	9(4.0%)
not withdrawn until D14	43(95.6%)	174(96.1%)	217(96.0%)

reason1: Withdrawal of informed consent
reason2: Adverse event
reason3: Investigator's judgement
reason4: Lost to follow-up(between study day1-4)
reason5: Death

Table 12-41: Adverse events (FAS)

	CQ (N=45)	CQ+MB (N=181)	Total (N=226)
Patients with at least one AE(1)	33(73.3%)	136(75.1%)	169(74.8%)
Number of AE's (=100%)	60(100.0%)	224(100.0%)	284(100.0%)
SAE			
- No			283(99.6%)
- Yes	0(0.0%)	0(0.0%)	1(0.4%)
Severity			
- mild			143(50.4%)
- moderate			139(48.9%)
- severe			2(0.7%)
Relationship			
- unrelated			163(57.4%)
- possibly related			120(42.3%)
- probably related	0(0.0%)	0(0.0%)	1(0.4%)
- definitely related	0(0.0%)	0(0.0%)	0(0.0%)
- cannot be assessed	0(0.0%)	0(0.0%)	0(0.0%)
MedDRA SOC			
- Gastrointestinal disorders	23(38.3%)	93(41.5%)	116(40.8%)
- Respiratory, thoracic and mediastinal disorders	16(26.7%)	78(34.8%)	94(33.1%)
- Infections and infestations	10(16.7%)	38(17.0%)	48(16.9%)
- Skin and subcutaneous tissue disorders	8(13.3%)	9(4.0%)	17(6.0%)
- Nervous system disorders	1(1.7%)	4(1.8%)	5(1.8%)
- Hepatobiliary disorders	0(0.0%)	2(0.9%)	2(0.7%)
- Metabolism and nutrition disorders	1(1.7%)	0(0.0%)	1(0.4%)
- Psychiatric disorders	1(1.7%)	0(0.0%)	1(0.4%)

(1) percent based on number of subjects by group; otherwise the percentages are based on the number of AE's by group.

Table 12-42: Adverse Events by WHO-Day (FAS)

	CQ (N=45)	CQ+MB (N=181)	Total (N=226)
AE by WHO-Day			
- D0	10(16.7%)	60(26.8%)	70(24.6%)
- D1	15(25.0%)	34(15.2%)	49(17.3%)
- D2	13(21.7%)	27(12.1%)	40(14.1%)
- D3	1(1.7%)	23(10.3%)	24(8.5%)
- D4-D12	13(21.7%)	59(26.3%)	72(25.4%)
- D14	8(13.3%)	21(9.4%)	29(10.2%)
Combination by WHO-Day			
- 111121	4(12.1%)	31(22.8%)	35(20.7%)
- 211111	2(6.1%)	15(11.0%)	17(10.1%)
- 121111	4(12.1%)	13(9.6%)	17(10.1%)
- 112111	4(12.1%)	9(6.6%)	13(7.7%)
- 221111	2(6.1%)	8(5.9%)	10(5.9%)
- 111112	2(6.1%)	7(5.1%)	9(5.3%)
- 211121	1(3.0%)	8(5.9%)	9(5.3%)
- 111211	0(0.0%)	8(5.9%)	8(4.7%)
- 211112	1(3.0%)	7(5.1%)	8(4.7%)
- 122111	2(6.1%)	3(2.2%)	5(3.0%)
- 111221	0(0.0%)	4(2.9%)	4(2.4%)
- 112121	1(3.0%)	3(2.2%)	4(2.4%)
- 221211	0(0.0%)	4(2.9%)	4(2.4%)
- 112211	0(0.0%)	3(2.2%)	3(1.8%)
- 121112	1(3.0%)	2(1.5%)	3(1.8%)
- 121121	2(6.1%)	1(0.7%)	3(1.8%)
- 212111	1(3.0%)	2(1.5%)	3(1.8%)
- 122121	2(6.1%)	0(0.0%)	2(1.2%)
- 211211	0(0.0%)	2(1.5%)	2(1.2%)
- 111122	1(3.0%)	1(0.7%)	2(1.2%)
- 212112	1(3.0%)	1(0.7%)	2(1.2%)
- 212221	0(0.0%)	1(0.7%)	1(0.6%)
- 221112	0(0.0%)	1(0.7%)	1(0.6%)
- 221121	1(3.0%)	0(0.0%)	1(0.6%)
- 111212	1(3.0%)	0(0.0%)	1(0.6%)
- 112112	0(0.0%)	1(0.7%)	1(0.6%)
- 211122	0(0.0%)	1(0.7%)	1(0.6%)

111211 means at least one AE on D3 but none on the other days

Table 12-43: Adverse Events by study day (FAS)

	CQ (N=45)	CQ+MB (N=181)	Total (N=226)
AE by Study day			
- D1	10(16.7%)	60(26.8%)	70(24.6%)
- D2	15(25.0%)	34(15.2%)	49(17.3%)
- D3	13(21.7%)	27(12.1%)	40(14.1%)
- D5-D13	1(1.7%)	23(10.3%)	24(8.5%)
- D5	17(28.3%)	66(29.5%)	83(29.2%)
- D14	4(6.7%)	14(6.3%)	18(6.3%)
Combination by Study day			
- 111112	1(3.0%)	2(1.5%)	3(1.8%)
- 111121	6(18.2%)	36(26.5%)	42(24.9%)
- 111122	0(0.0%)	1(0.7%)	1(0.6%)
- 111211	0(0.0%)	8(5.9%)	8(4.7%)
- 111221	1(3.0%)	4(2.9%)	5(3.0%)
- 112111	4(12.1%)	9(6.6%)	13(7.7%)
- 112112	0(0.0%)	1(0.7%)	1(0.6%)
- 112121	1(3.0%)	3(2.2%)	4(2.4%)
- 112211	0(0.0%)	3(2.2%)	3(1.8%)
- 121111	4(12.1%)	13(9.6%)	17(10.1%)
- 121112	1(3.0%)	2(1.5%)	3(1.8%)
- 121121	2(6.1%)	1(0.7%)	3(1.8%)
- 122111	2(6.1%)	3(2.2%)	5(3.0%)
- 122121	2(6.1%)	0(0.0%)	2(1.2%)
- 211111	2(6.1%)	15(11.0%)	17(10.1%)
- 211112	0(0.0%)	6(4.4%)	6(3.6%)
- 211121	2(6.1%)	9(6.6%)	11(6.5%)
- 211122	0(0.0%)	1(0.7%)	1(0.6%)
- 211211	0(0.0%)	2(1.5%)	2(1.2%)
- 212111	1(3.0%)	2(1.5%)	3(1.8%)
- 212112	1(3.0%)	0(0.0%)	1(0.6%)
- 212121	0(0.0%)	1(0.7%)	1(0.6%)
- 212221	0(0.0%)	1(0.7%)	1(0.6%)
- 221111	2(6.1%)	8(5.9%)	10(5.9%)
- 221112	0(0.0%)	1(0.7%)	1(0.6%)
- 221121	1(3.0%)	0(0.0%)	1(0.6%)
- 221211	0(0.0%)	4(2.9%)	4(2.4%)

112111 means at least one AE on day3 but none on the other days