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Dose finding for a safe and efficacious combination of chloroquine and methylene blue in the treatment of uncomplicated falciparum malaria in young children of Burkina Faso (ISRCTN36731786)

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3 ABBREVIATIONS

ACPR	adequate clinical and parasitological response (not CPF)
AE	adverse event
CHI	Chi-square (continuity corrected)
CI	confidence interval
C_{max}	maximum concentration
CQ	chloroquine
CPF	clinical or parasitological failure (ETF or LCF or LPF)
CRF	case report form
CRSN	Nouna Health Research Centre
ETF	early treatment failure
FAS	full analysis set (an analysis population)
Hb	haemoglobin
Hct	haematocrit
IMBI	Institut für Medizinische Biometrie und Informatik
LCF	late clinical failure
LPF	late parasitological failure
LR	likelihood ratio (test)
ITT	intention to treat
MB	methylene blue
PCR	polymerase chain reaction
PP	per protocol (an analysis set)
RAE	relevant AE
SAE	serious AE
SAF	safety population (an analysis population)
SOC	system organ class (MedDRA coding)
SSA	Sub-Saharan African
TF	treatment failure (ETF or LCF)
T_{max}	Time of maximum concentration
WMW	Wilcoxon Mann Whitney (U-Test)
WSR	Wilcoxon sign rank

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 because Methylene blue (MB) has a similar mode of action as chloroquine (CQ) and is also cheaply available.

Objectives: The primary objective of this study was to evaluate a efficacious dose of CQ-MB and to investigate whether there is any improvement having 4 instead of 2 drug intakes per day.

Methods: In this hospital-based randomized controlled trial (ISRCTN36731786), 435 children (6-59 months) with uncomplicated falciparum malaria were treated in Burkina Faso. All study children received a total dose of 25mg/kg of CQ over a period of three days. The children were randomized to 2 or 4 times (2 groups) MB intake per day with 36, 54, or 72 mg/kg (3 levels). Primary outcome were the incidence of relevant adverse events and treatment failures. Patients were hospitalised for 4 days and followed-up until day 14.

Results: Three relevant adverse events occurred of which one was probably attributed to the study medication. In the per protocol analysis, there were no dose or group specific effects. Overall clinical and parasitological failure rates by day 14 were 10% [95% CI (7.5%, 14.0%)] and 24% [95% CI (19.4%, 28.3%)] respectively.

Conclusion: MB in combination with CQ appears to be safe and effective against malaria in Africa, but given its short half life and the high background resistance against CQ a more effective partner drug needs to be identified.

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). Although a small number of new malaria drugs including artemisinin derivates have been developed in recent years, these are usually too expensive for unsubsidised use in SSA.

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, Mandi et al. 2005, Meissner et al. 2005).

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).

In our previous studies, the oral combination of CQ and MB has been shown to be safe in adults and children of Burkina Faso with and without G6PD deficiency. However, using 4 mg/kg/day of MB in the combination was not sufficiently effective against malaria in our study children (Meissner et al. 2005). As there are published observations in adults and children showing that MB has been safe and effective in dosages 10 times higher than in our studies, and MB often was given in these studies in several daily doses and over prolonged periods of time (up to several weeks), it appears promising and justified, to increase the MB dose stepwise until the desirable therapeutic efficacy is reached, unless there are unexpected safety problems which would be prohibitive of further dose increments.

The primary objective of this study was therefore to determine a safe and effective dose (36, 54, 72, or 168 mg/kg) and dosing regimen (2x versus 4x daily) of MB for co-administration with a conventional dose of CQ as an affordable new drug combination for the treatment of uncomplicated falciparum malaria in western African children.

6 MATERIAL AND METHODS

6.1 Study area and study subjects

The study was conducted in July until November 2004 in the District Hospital of Nouna in the province of Kossi in north-western Burkina Faso. In June/July 2004, the community was informed, field staff was trained, and pilot testing of methods took place. 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).

Children with Burkinabe nationality aged 6-59 months with uncomplicated falciparum malaria (axillary temperature $\geq$ 37.5°C and $\geq$ 2.000 P. falciparum asexual parasites per µl blood) whose parents or caretaker had given informed consent were enrolled into the study. Children with complicated or severe malaria (repeated vomiting, seizures or other neurological impairment), hyperparasitaemia (>100000 /µl) 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 primary objective of this study was to determine a safe and effective dose (36, 54, 72, or 168 mg/kg) and dosing regimen (2x versus 4x daily) of MB for co-administration with a conventional dose of CQ as an affordable new drug combination for the treatment of uncomplicated falciparum malaria in western African children.

The secondary objectives of this study were:

- to compare efficacy of a twice daily dose regimen with a four times daily dose regimen.
- to study the pharmacokinetics of the combination of CQ-MB in children with uncomplicated falciparum malaria in western Africa

6.3 Primary endpoints

Composite primary endpoint:

1. Incidence of *relevant* adverse events
2. Incidence of treatment failures (TF)

Justification: The composite primary endpoint will be used mainly for the decision to go ahead with the next dose level or to stop the dose finding (see design of the trial, chapter 6.5).

6.4 Secondary endpoints

- Incidence of early treatment failure (ETF)
- Incidence of late clinical failures (LCF)
- Incidence of late parasitological failures (LPF)
- Incidence of late parasitological failures (CPF)
  (post hoc: not mentioned as secondary endpoint in the protocol)
- Fever clearance time
- Parasite clearance time
- Change in haemoglobin after 4 (or 7) and 14 days compared to baseline
- Incidence of observed serious adverse events over the 14 days observation period (safety, not mentioned as secondary endpoint in the protocol)
- Incidence of observed and self-reported non-serious adverse events over the 14 days observation period
- Whole blood CQ and MB kinetics (mean AUC, C_{max}, T_{max}, elimination half life)
- Monitoring of concomitant drug intake
- G6PD assessment based on PCR

Table 6-1: Definitions

Term	Definition
Age	If a full date of birth is known, the exact age can be calculated using the date of informed consent and date of birth. If the actual day of the birth date is unknown, it is set to 15. If day and month are missing the 1st of July is considered as the date of birth.
Baseline values	Directly after the written informed consent a blood sample will be taken for the baseline measurements (Laboratory baseline values). Those values are considered as baseline values.
Change under treatment	Any change under treatment is defined as post-baseline value minus baseline value. If more than one value is available the last value will be taken for the difference.
D0, D1, D2, D3	For the definition of days the latest WHO Definition is used (WHO 2003). The day that the patient is enrolled and receives the first dose of medicine is designated as D0. Thereafter, the schedule follows with D1, D2, etc. D0=[0h, 24h], D1=(24h, 48h], D2=(48h, 72h], D3=(72h, 96h]
D14	For this analysis we define D14 as the 14^{th} day after first drug intake, but with the tolerance of –1 and +3 calendar days. D14=(312h, 432h]
D28	For this analysis we define D28 as the 28^{th} day after first drug intake, but with the tolerance of –3 and +3 calendar days. D28=(600h, 768h]
G6PD-deficiency	A subject is considered G6PD-deficient for the current study in case of a positive result of a diagnostic test (modified Beutler-Mitchell-Test) carried out on blood samples taken for baseline measurement prior to administration of study drugs. The G6PD status was analyzed only in case of clinical decisions.
Severe acute haemolysis	Haemoglobin ≤ 5 g/dl or received blood transfusion according to clinical judgement of study physician.
Severe methaemo-globinaemia	Methaemoglobin > 25%
Severe acute neurological disorder	Acute change in consciousness, ≥ 2 convulsions
AEs	The adverse event (=AE) defined in the protocol is used, but blue urine is expected for all children in the CQ+MB treatment group and it is not considered as an adverse event for the analysis. Only AEs after initiation of study treatment will be tabulated (ICH-E3).
Relevant adverse event	If one of the following criteria is fulfilled between the first drug intake and 24h after the last drug intake. • Acute haemolysis

Term	Definition
	• Methaemoglobinaemia • Severe acute neurological disorders possibly, probably, or definitely related to the study drug • Study drug related SAE
Severe malaria	A patient is counted as having severe malaria if one of the following criteria is fulfilled (WHO 2003) • Prostration (inability to sit upright in a child normally able to do so, or to drink in the case of children too young to sit) • Impaired consciousness • Respiratory distress (acidotic breathing / severe acidosis) • Multiple convulsions • Circulatory collapse • Pulmonary oedema • Abnormal bleeding • Jaundice (= Hyperbilirubinemia) • Haemoglobinuria • Severe anaemia (Hb < 5g/dl) • Hyperparasitaemia (>500.000/µl) • Persistent vomiting
Parasitaemia	Positive measurement of *P. falciparum* with or without *P. ovale* and *P. malariae*
ETF	A patient is counted as early treatment failure (=ETF) if *one* of the following criteria is fulfilled (WHO Definition). • Development of danger signs (clinically defined, based on judgement of study physicians) on D1-D3 in the presence of parasitaemia. • Severe malaria on D1-D3 • D2: parasites > baseline count • D3: Fever (≥37.5°C) and parasitaemia (parasites > 0) • D3: ≥ 25% of baseline parasites
LCF (14, WHO)	A patient is not an ETF and is counted as late clinical failure (=LCF) if *one* of the following criteria is fulfilled (WHO Definition). • Development of danger signs (clinically defined, based on judgement of study physicians) on D4-D14 in the presence of parasitaemia • Severe malaria on D4-D14

Term	Definition
	• Fever (≥37.5°C) and parasitaemia > 0 on D4-D14
LCF (28,WHO)	See LCF (14, WHO), only the time periods are different: D4-D28 instead of D4-D14. Therefore all patients which are LCF (14, WHO) are LCF (28, WHO) as well.
TF (14, WHO)	A patient is considered as treatment failure (day 14) if he/she is ETF *or* LCF(14,WHO) (WHO Definition).
TF (28, WHO)	A patient is considered as treatment failure (day 28) if he/she is TF(14) *or* LCF(28) (WHO Definition).
LPF (14, WHO)	A patient who is not ETF or LCF(14, WHO) earlier is considered as late parasitological failure in case of parasitaemia > 0 on D14 and a measured temperature < 37.5°C (WHO Definition).
LPF (28, WHO)	A patient (only for the third dose level) who is not ETF or LCF(14,WHO) earlier is considered as late parasitological failure (28) in case of: parasitaemia > 0 on D7-D28 and a measured temperature < 37.5°C.
CPF (14, WHO)	A patient is considered as clinical or parasitological failure (day 14) if he/she is ETF *or* LCF(14,WHO) *or* LPF(14, WHO). (ETF+LCF+LPF=1-ACPR)
CPF (28, WHO)	A patient is considered as clinical or parasitological failure (day 28) if he/she is ETF *or* LCF(28,WHO) *or* LPF(28, WHO). (ETF+LCF+LPF=1-ACPR)
ACPR (14, WHO)	Absence of parasitaemia on D14 irrespective of axillary temperature without previously meeting any criteria of ETF, LCF (14, WHO) or LPF (14, WHO).
ACPR (28, WHO)	Absence of parasitaemia on D28 irrespective of axillary temperature without previously meeting any criteria of ETF, LCF (28, WHO) or LPF (28, WHO).
Fever clearance time	time from begin of treatment to the first of two consecutive measurements of an axillary temperature < 37.5°C during the full hospitalization (D0-D3) time of the child
Parasite clearance time	time from begin of treatment to the first time when the parasitaemia is not detectable anymore during the full hospitalization time (D0-D3) of the child

ETF=1 =>	LCF(14) =0,	LPF(14)=0,	LCF(28)=0,	LPF(28)=0 ,	TF(14)=1,	TF(28)=1,	ACPR(14)=0,	ACPR(28)=0
ETF=0,	LCF(14) =1 =>	LPF(14)=0,	LCF(28)=1,	LPF(28)=0 ,	TF(14)=1,	TF(28)=1,	ACPR(14)=0,	ACPR(28)=0
ETF=0,	LCF(14) =0,	LPF(14)=1 =>	LCF(28)=0,	LPF(28)=1 ,	TF(14)=0,	TF(28)=0,	ACPR(14)=0,	ACPR(28)=0
ETF=0,	LCF(14) =0,	LPF(14)=0,	LCF(28)=1 =>	LPF(28)=0,	TF(14)=0,	TF(28)=1,	ACPR(14)=1,	ACPR(28)=0
ETF=0,	LCF(14) =0,	LPF(14)=0,	LCF(28)=0	LPF(28)=1 =>	TF(14)=0,	TF(28)=0,	ACPR(14)=1,	ACPR(28)=0
ETF=0,	LCF(14) =0,	LPF(14)=0,	LCF(28)=0	LPF(28)=0 =>	TF(14)=0,	TF(28)=0,	ACPR(14)=1,	ACPR(28)=1

with: 1=failure, 0=no failure

Comment: All patients are ETF, LCF(14), LPF(14) *or* ACPR(14). Additionally in the third level all patients are ETF, LCF(28), LPF(28) *or* ACPR(28).

Comment: PCR information of recrudescence regarding day 28 for level 3 was added (only the same type/stream of p.faliciparum) or reinfection (with a new type/stream of p.falciparum): A patient who was initially LCF (or LPF) becomes a no LCF (or no LPF) if *only* new streams of p.falciparum can be found via PCR method at day 14 or 28 respectively. Only in 5 patient were only new streams found (409, 412, 456, 505, 521), the first 3 were already treatment failures until day 14; the other two were considered as ACPR(28) instead of failures.

6.5 Study design

Single-centre, uncontrolled trial on the safety and efficacy of CQ in fixed doses combined with increasing total doses of MB given in two different dosage regimens, A and B, intending either to achieve high maximum concentration or inhibitory maintenance concentrations of MB (parallel and randomised) in young children of Nouna Health District, north-western Burkina Faso. The 1:1 randomisation into the two groups per dose level was implemented using a computer generated randomisation list (block randomisation) created in Heidelberg. Telephone or fax randomisation was not feasible due to the instable communication system.

The dose escalation process for a dosage regimen group went into the next higher dose level if

1. the safety aspect was fulfilled (i.e. one-sided 95% confidence interval for the incidence of relevant AEs below 0.1) and
2. the efficacy criterion (i.e. one-sided 95% confidence interval for the incidence of TF below 0.15) was fulfilled at most in one dose level. I.e. the mentioned criterion had to be confirmed in a second dose level to conclude efficacy.

The process stopped if one of the two criteria was not fulfilled or the highest dose level was reached. Formally the safety scoring group had to decide whether to proceed to the next level or not. All people in this group were fully integrated in the trial process, therefore a quick decision was expected. In case of not finding a common consensus the DSMB was involved.

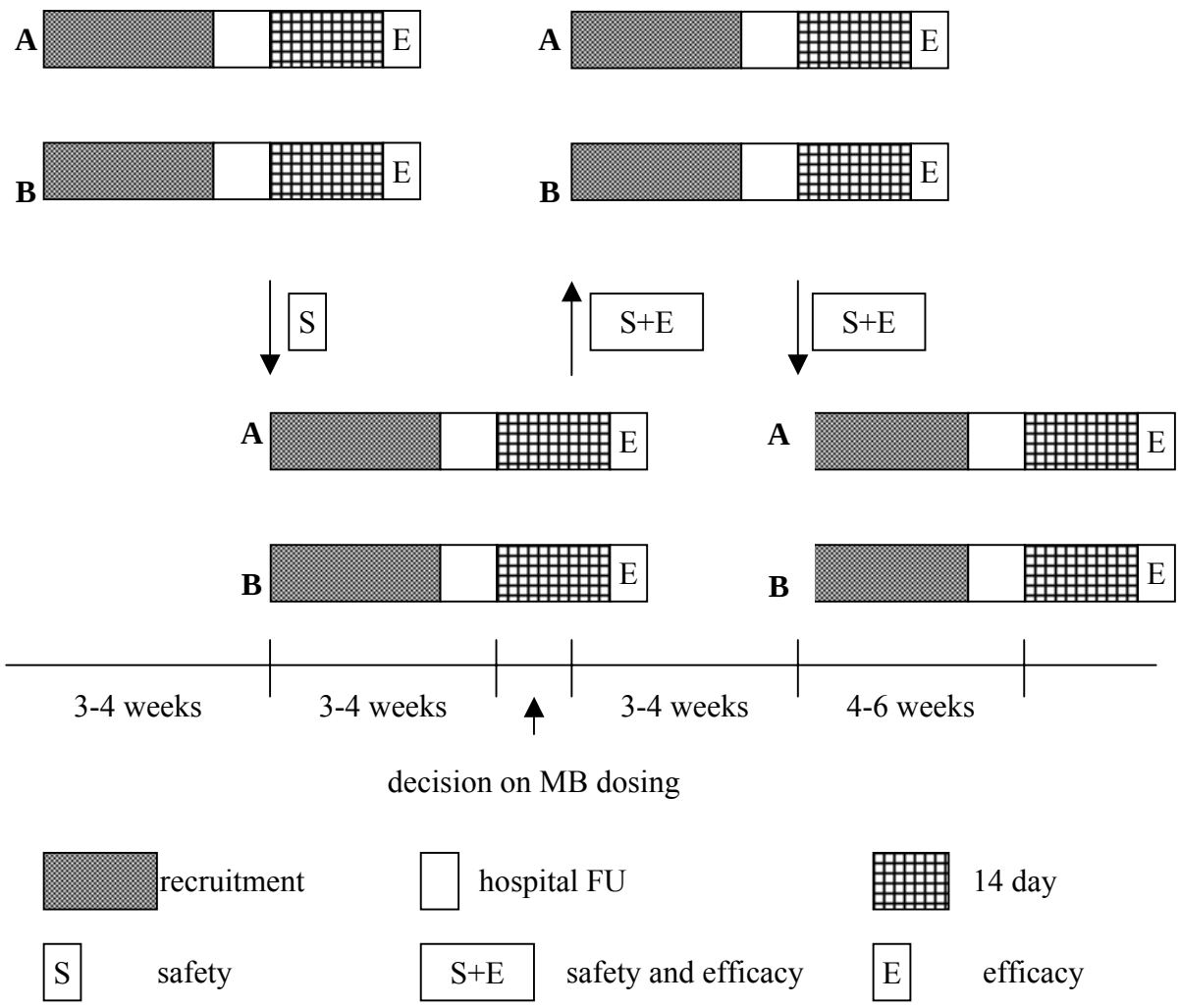

Figure 6-1: Project flow with dose escalation

6.6 Laboratory work-up

Venous blood samples were taken. Determination of Hb, methaemoglobinaemia and malaria parasitaemia will be done in the laboratory of CRSN with routine methods. From the baseline blood, an EDTA blood sample will be stored for phenotypical emergency G6PD deficiency determination in case of acute haemolysis (modified Beutler-Mitchell test). A filterpaper blood sample will be stored for retrospective genotypical determination of G6PD status in Germany. For assessing possible correlations between safety and efficacy of the study treatments and the population kinetics of the study drugs, whole blood concentrations of CQ and MB will be

determined in all study participants on day 3 from dried filter paper samples. Drug concentrations will be determined by HPLC and mass spectrometry methods recently developed, and will be the basis for calculation of population kinetics (AUC, C_{max}, T_{max}, elimination half life). More information see trial protocol.

6.7 Sample size justification

The study had a sequential character and should show with sufficient power (80%) if there is an efficient and safe CQ+MB regimen. In case of no safe CQ+MB regimen the study should be stopped with a clear evidence for an unsafe CQ+MB regimen.

In a first calculation it was assumed that the safety and efficacy endpoint are independent of each other. This allows explicit calculation of the probability for different study outcomes. For sample size calculation three overall outcomes are considered: S – the study was stopped because of a safety failure; E – the study was stopped because of evidence for sufficient efficacy; U – the study was stopped because of an indecisive situation (no safety failure or no proof of efficacy).

In the following, the Null hypothesis for the probability of a relevant adverse event p_S is set to $H_{0,Safety}$: $p_S \geq 0.1$. Two possible Null hypotheses for the probability of a treatment failure p_E will be considered: $H_{0,Efficacy\ I}$: $p_E \geq 0.1$ and $H_{0,Efficacy\ II}$: $p_E \geq 0.15$.

As sample size for a dose regimen the following numbers are considered: N=60, 65, 70.

The following safety and efficacy scenarios for the sequence of for studies are considered. A scenario is described by two vectors p_S, p_E which describe the level specific safety and treatment failure rates. The first number of a vector belongs to level 1, ... , the fourth number of a vector belongs to level 4.

Scenario I describes a situation of increasing loss of safety and marginal efficacy:

p_S = (0.015, 0.025, 0.050, 0.100)

p_E = (0.100, 0.100, 0.100, 0.100)

Scenario II describes a situation of increasing loss of safety and increasing efficacy:

p_S = (0.015, 0.025, 0.050, 0.100)

p_E = (0.050, 0.025, 0.015, 0.015)

Scenario III describes a situation of insufficient safety and insufficient efficacy:

p_S = (0.10, 0.10, 0.10, 0.10)

p_E = (0.15, 0.15, 0.15, 0.15)

Scenario IV describes a situation of sufficient safety and marginal efficacy:

p_S = (0. 015, 0. 015, 0. 015, 0. 015)

p_E = (0.100, 0.100, 0.100, 0.100)

Scenario V describes a situation of sufficient safety and increasing efficacy:

p_S = (0.015, 0.015, 0.015, 0.015)

p_E = (0.100, 0.050, 0.025, 0.025)

An appropriate study size and testing strategy should result in the following decisions:

Scenario I: Study should stop before arriving in the highest dose regimen.

Scenario II: Stop study early enough in low dose levels with sufficient safety

Scenario III: Stop study because safety and efficacy are not given

Scenario IV: Study should not stop because of safety failure but may end indecisive with respect to efficacy

Scenario V: Study should detect this scenario as one with enough efficacy and safety.

The following table summarises the probabilities for the three study outcomes (S – the study was stopped because of a safety failure; E – the study was stopped because of evidence for sufficient efficacy; U – the study was stopped because of an indecisive situation (no safety failure or no proof of efficacy) for the three sample sizes and two testing strategies for efficacy under consideration.

Table 6-2: Simulations for the sample size calculation

N	Scenario	$H_{0,\ Efiicacy\ I}$: $p_E \geq 0.10$			$H_{0,\ Efiicacy\ II}$: $p_E \geq 0.15$		
		S	E	U	S	E	U
60	I	0.699	0.000	0.301	0.670	0.119	0.211
	II	0.644	0.204	0.152	0.524	0.464	0.012
	III	1.000	0.000	0.000	1.000	0.000	0.000
	IV	0.643	0.000	0.356	0.615	0.135	0.251
	V	0.634	0.047	0.319	0.507	0.452	0.041
65	I	0.340	0.005	0.655	0.328	0.140	0.531
	II	0.277	0.553	0.170	0.228	0.749	0.023
	III	1.000	0.000	0.000	1.000	0.000	0.000
	IV	0.266	0.006	0.729	0.256	0.152	0.591
	V	0.237	0.398	0.366	0.199	0.700	0.101
70	I	0.510	0.002	0.489	0.481	0.188	0.330
	II	0.426	0.440	0.134	0.348	0.641	0.011
	III	1.000	0.000	0.000	1.000	0.000	0.000
	IV	0.309	0.003	0.688	0.290	0.245	0.466
	V	0.278	0.360	0.362	0.211	0.754	0.035

Probability of study outcome (S, E, U) under different sample sizes (N=60,65,70) and testing strategies (I, II)

Simulations were also done assuming correlation between the safety and efficacy outcome. The simulation do not show substantial deviation from the results calculated for the independence model.

Table 6-2 shows, that the sample size 60 has not enough power (~37 % under $H_{0,\ Efiicacy\ I}$: $p_E \geq 0.10$ and ~ 50% under $H_{0,\ Efiicacy\ II}$: $p_E \geq 0.15$) to detect the relevant scenario V. For sample size 65 and under $H_{0,\ Efiicacy\ II}$ the power is ~80% to prove the safety aspect. The chance to end up with an efficacy result is 70% for this setting. Also for scenario IV there is a high probability (~75%) not to end up with a safety failure. Scenario I and scenario II are also covered with sufficient statistical quality. Changing the Null hypothesis for efficacy to $H_{0,\ Efiicacy\ I}$ would create disadvantage for scenario V. The advantages gained through a higher sample size (N=70) are not substantial.

Therefore, it is recommended to include 65 patients per dose level in each arm. Assuming 10% drop outs results in a sample size of 72 children per dose level in each arm. This sums up to a total sample size of 576 children.

6.8 Statistics

6.8.1 Analysis of the primary endpoint

The significance level (type I error) for all analysis was set to 0.05. The two primary endpoints were tested hierarchically. Therefore, no adjustments for multiple tests were necessary. The analysis was done for the FAS. The PP set was used as sensitivity analysis. Each of the safety and efficacy test of hypotheses will be performed per dosage regimen and dose level. The so called efficacy test is not a classical test versus placebo but a test against an a priori specified margin (here 15%). Further comparisons between groups and levels were done exploratory, see below. The hypotheses by group and level were as follows:

1. $H_{0,Safety}: p_S \geq 0.1$ versus $H_{1,Safety}: p_S < 0.1$
2. $H_{0,Efficacy}: p_E \geq 0.15$ versus $H_{1,Efficacy}: p_E < 0.15$

where p_S denotes the incidence of RAE and p_E the incidence of TF(14, WHO). The tests were performed using exact one-sided 95% confidence intervals for the incidences of RAE or TF respectively.

6.8.2 Analysis of the secondary endpoints

All analyses for the secondary analyses have explorative character. Descriptive statistics, 95% confidence intervals, Wilcoxon-Mann-Whitney tests (U-Test, WMW), continuity corrected Chi-Square tests (Chi), Kruskal-Wallis tests (KW), Wilcoxon-Sign-Rank test (WSR), F-Tests / Wald tests (F) or Likelihood-Ratio tests (LR) in case of parametric models, Chi-Square tests (Cox) in case of time to event analyses were used.

In case of time to event analyses (fever clearance, parasite clearance) a Cox model was used with interaction group*level (SAS procedure phreg). The interaction was eliminated in case of a corresponding p-value above 0.2. The two main effects group and level left in the model. No further covariates were used.

In case of the treatment failure rates a logistic model was used with interaction group*level (SAS procedure logistic, LR-Tests). The interaction was eliminated in case of a corresponding p-value above 0.2. The two main effects group and level left in the model. No further covariates were used.

In case of the analysis of the changes of Hb from baseline (day 4 – baseline, day 14 – baseline) a linear regression model was used with interaction group*level (SAS procedure glm, F-Tests). The

interaction was eliminated in case of a corresponding p-value above 0.2. The two main effects group and level left in the model. No further covariates were used.

6.8.3 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.

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

6.8.4 Software

Evaluations were carried out using the software package SAS® System 8.2 or 9.1 (SAS Inc., Cary/NC, USA).

6.9 Defintions of analysis populations

Two analysis sets will be defined: the Safety Set (SAF) and Full Analysis Set (FAS) are identical in this trial and the Per-Protocol Set (PP).

- 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 (ITT).
- Per-Protocol (PP) Set (SAS variable `pp_extra`): This analysis set will consist of all patients included in the full analysis set and treated on D0-D2: twice per day for patients in the group 2x and four times per day for patients in the group 4x. 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 without blue urine
    - Patients who dropped out early (before day 14)

- Patients without information on D14
- Patients treated (D4-D13) with although no fever and/or no parasites

Patients who got the wrong concentration could have been excluded as well but they were not. There were 36 children who got a higher dose than intended at level 1 which was conservative for decision making. However, in some situations the subgroup of "patients in PP with correct dose" (PP set in the strong sense) was considered (SAS variable pp).

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.

Depending on the dose level, doses of MB of 36, 54, and 72 mg/kg were given respectively. The fourth dose level with 168 mg/kg was not performed (see chapter 7.1). At each dose level children were randomized to two or four MB doses per day (2x versus 4x daily). MB (Mayrhofer Pharmazeutika, Linz/Austria) was given as a 1.77% or 2.4 % solution with fruit flavouring and honey supplement to mask the bitter taste.

Administration of study medications was directly supervised by a study physician or a study nurse and in case of vomiting within 30 minutes, the drugs were one-time re-administered.

Study participants were hospitalized for 72 hours. At least once during the time of hospitalisation the colour of the urine was checked to assess MB compliance through visual observation. Children were systematically examined on day 0, 1, 2, 3, 4, 14 (and day 28 in level 3). Blood samples were processed with standard methods in the *Centre de Recherche en Santé de Nouna* (CRSN). Methaemoglobin formation was monitored twice daily on day 0 and once on day 1, 2 and 3. Other laboratory parameters like liver enzymes, serum creatinine or the phenotypical G6PD status were available at any time if clinically indicated. Based on filter paper blood samples, the G6PD genotype was determined in Germany.

All children having fever ≥ 38.5°C received standard doses of paracetamol (= acetaminophen; 10 mg/kg every 6 hours) until symptoms subsided (taken from the essential drug stock of the Ministry of Health, product description: paracetamol tablets).

All indicated drugs were allowed, except other western antimalaria drugs, antibiotics with antimalarial efficacy, dapsone and other sulfones, acetanilide and phenacetin, nalidixic acid, niridazole, nitrofurantoins and sulphonamides from beginning of treatment until end of follow-up.

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" (CPMP 1997). 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 scoring group decided whether to proceed to the next level or not. The safety of the trial was also monitored by a data safety monitoring board (DSMB). The statistical site was at the IMBI. The statistical analysis of this study was carried out by the independent statisticians Prof. Dr. Ulrich Mansmann and Dr. Steffen Witte. It was the responsibility of the independent statisticians to ensure that all relevant statistical aspects were considered. From the investigator site in Nouna Théophile Tapsoba was involved.

- Sponsor: DSM Fine Chemicals Austria
- Principal investigator: PD Dr. med. Olaf Müller
- Biometricians: Prof. Dr. rer. nat. Ulrich Mansmann (responsible) and Dr. sc. hum. Steffen Witte
- Trial Coordinator in Germany: Dr. med. Peter Meissner, MSc Trop Paed
- Trial Coordinator in Burkina Faso: Dr. Bocar Kouyaté, MPH
- Study team (alphabetical order): Dr. rer. nat. Jürgen Burhenne, Dipl. Biol. Boubacar Coulibaly, Dr. Mandi Germain, PD Dr. med. Albrecht Jahn, Prof. Dr. rer. nat. Ulrich Mansmann, PD Dr. med. Dipl. Phys. Gerd Mikus, PD Dr. med. Olaf Müller, Dr. med. Jens Rengelshausen, Dipl.-Ing.(FH) Klaus-Dieter Riedel, Dr. rer. nat. Wolfgang Schiek, Prof. Dr. med. Heiner Schirmer, Théophile Tapsoba, Prof. Dr. med. Ingeborg Walter-Sack, Dr. sc. hum. Steffen Witte

- Steering Committee: PD Dr. med. Olaf Müller, PD Dr. rer. nat. Ulrich Mansmann, Prof. Dr. med. Ingeborg Walter-Sack, Dr. rer. nat. Wolfgang Schiek, Dr. Bocar Kouyaté
- Scientific advisory Board (SAB): PD Dr. med. Christoph Hatz, Prof. Dr. med. Walter E. Haefeli, Prof. Dr. med. Katja Becker-Brandenburg
- Safety scoring group: Dr. Bocar Kouyaté, Dr. Mandi Germain, PD Dr. Olaf Müller, Prof. Dr. Ingeborg Walter-Sack, Dr. Peter Meissner
- Data safety monotoring board (DSMB): Prof. Dr. rer. nat. Heiko Becher, Dr. med. August Stich, Prof. Dr. Innocent Pierre Guissou

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. 2006). 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 enrolled on the 21st of July 2004, the last on the 31st of October 2004 (Table 7-1). In total 435 children with uncomplicated malaria were enrolled (Figure 7-1, Table 12-1).

Table 7-1: Date of enrolment by dose level

Dose Level	First patient enrolled	Last patient enrolled	Last visit done
1	21 July 2004	19 Aug 2004	1 Sept 2004
2	24 Aug 2004	23 Sept 2004	6 Oct 2004
3	30 Sept 2004	31 Oct 2004	26 Nov 2004
4	none	none	none

There was no formal stop of patient recruitment fulfilled (neither the safety criteria nor the efficacy criteria was fulfilled, see chapter 7.6). However, the recruitment was stopped nearly at the end of the third dose level in the end of October 2004 due to the end of the malaria season. Not enough children could have been enrolled in the end of the year.

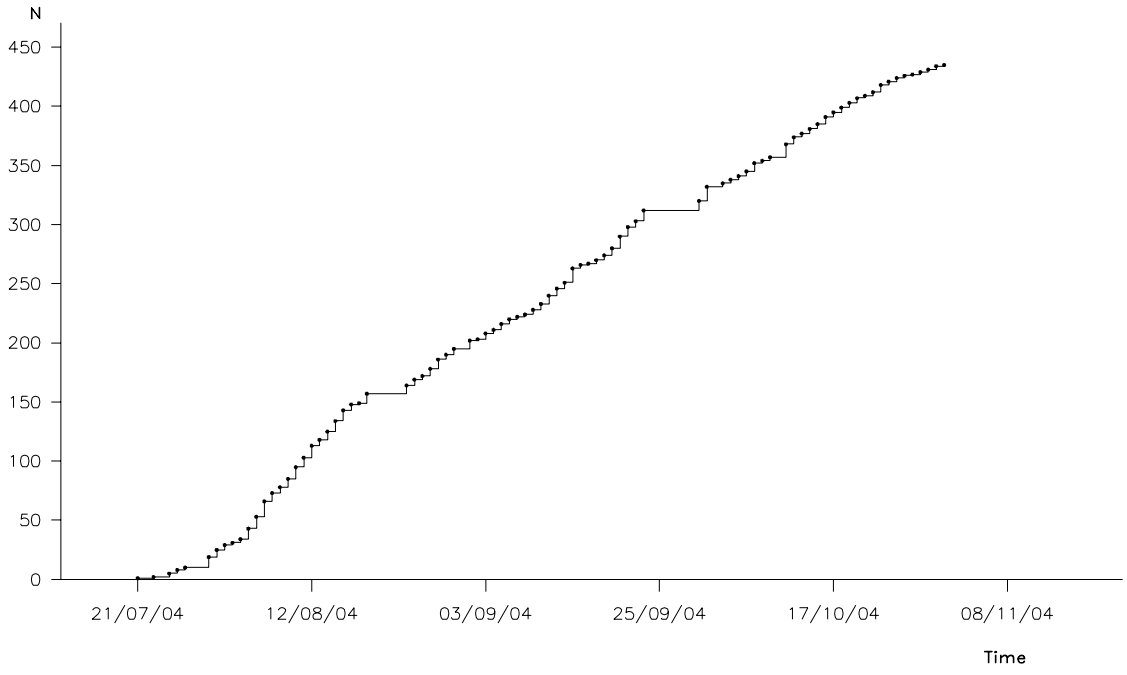

Figure 7-1: Recruitment of patients

7.2 Analysis Sets and Compliance

Out of the 435 enrolled children 20 (4.6%) were excluded from the full analysis set due to repeated vomiting (no trial medication, level 1: 10, level 2: 2, level 3: 8), and 3 children (all in level 2) did

not receive any trial medication due to other reasons. Therefore 412 patients (2x daily: 197, 4x daily 215) were in the a priori defined full analysis set for the intention to treat analysis.

Out of those 412 patients 48 were not in the per-prococol set due to various reasons (Table 12-2 to Table 12-5), mainly due to vomiting (14 children) or due to missing information on D14/D28. Therefore the per-protocol set for the PP analysis consists of 364 (2x daily: 173, 4x daily 191) patients, see Figure 7-2.

Out of the 364 patients there were 36 children who got a higher dose than intended at level 1 (104-118, 120-125, 127, 129-131, 133-143). One patient (119) in the FAS got also a wrong concentration but was not in the PP set anyway.

The mean time from baseline blood measurement to the first treatment was 2.0 +/– 0.7h (2x daily) and 2.0 +/– 0.6h (4x daily) with a total range of 0.5 to 5.2h and therefore much shorter than in the former trial (CQ: 7.8 +/– 2.3h, CQ-MB: 7.4 +/– 2.5h) (Witte et al. 2006), see Table 12-17 and Table 12-14 for level 1, Table 12-15 for level 2, and Table 12-16 for level 3.

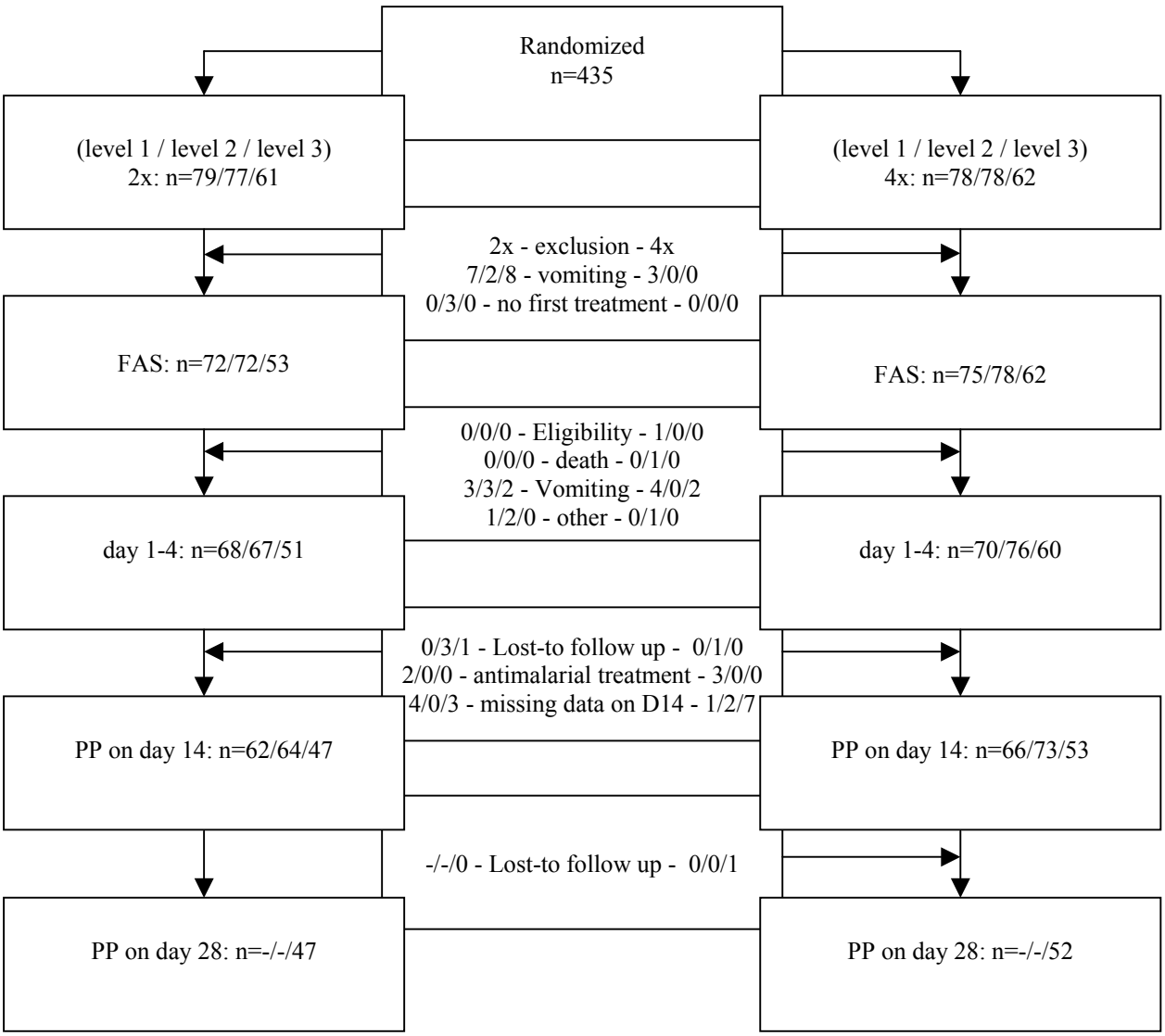

Figure 7-2: Flow chart of patients

7.3 Quality of Data

Double data entry was performed in Nouna. Inconsistencies were checked generating queries. In total 242 inconsistency checks were programmed. The investigators solved all queries. The data base was first closed in January 2005 and reopened on the 17th of February, 9th of March, 29th of March, 26th of April, 21st of July, and 12th of December 2005 due to minor changes. No formal monitoring was done. The final analysis run in May 2005.

7.4 Demographic characteristics of study subjects

Out of 412 children 218 (52.9%) were boys. The mean age was 33.3 +/– 15.1 months (range: 6 to 59). The average weight was 12.1 +/– 3.0 kg (range: 5 to 20). Other prior illnesses were captured for 21.7% of the children. The current malaria disease episode when the patients was enrolled was on average 2.2 +/– 1.1 days (range: 1 to 14). Nearly one third (30.3%) of the patients had any prior treatment of the current disease episode. In total there were 321 (78.5%) children with G6PD sufficient (PCR method), 50 (12.2%) heterozygote deficient, and 38 (9.3%) homozygote deficient (3 missing values). The statistics were presented for all patients in the FAS, over both groups and all three dose levels.

The two groups were comparable, the randomization was successful (Table 12-9).

Comparing the levels (two groups pooled) there was no difference found regarding sex (p_{Chi}=0.6384), weight (p_{KW}=0.1125), and G6PD deficiency (p_{Chi}=0.1274). But there were differences between the levels regarding age (p_{KW}=0.0124) with an increasing age from level to level (level 1: 31.6 months, level 2: 32.1 months, level 3: 36.9 months), length of the current disease episode (p_{KW}<0.0001) with a shorter mean episode in the first level (level 1: 1.9 days, level 2: 2.5 days, level 3: 2.3 days), other prior illnesses (p_{Chi}=0.0081) with a higher rate in the second level (level 1: 14.5%, level 2: 29.3%, level 3: 20.9%), and prior treatment of the current disease episode (p_{Chi}=0.0233) with a decrease from level to level (level 1: 37.4%, level 2: 30.0%, level 3: 21.7%). The descriptive statistics were presented by level in Table 12-6 for level 1 Table 12-7 for level 2 and Table 12-8 for level 3. Due to the sequential character of the design no randomization between level was possible. Some imbalances between the levels were therefore expected. Post-hoc sensitivity analyses were not done.

The prevalence of the genetic resistance for CQ (pfcrt T76) is 52.6% (3 missings), comparable between groups (p_{Chi}=0.3186, 2x daily: 50.0%, 4x daily: 54.9%) but not between levels (p_{Chi}<0.0001) with increasing resistance from level to level (level 1: 39.0%, level 2: 56.0%, level 3: 65.5%).

7.5 Laboratory baseline data

Mean haemoglobin [g/dl] at baseline was 9.6 +/– 1.0 (range: 6.9 to 14.2), mean methaemoglobin [g/dl] was 1.2 +/– 0.5 (range: 0.2 to 2.9). The median parasite density (P. faliciparum) was 24800 (range: 1050 to 100000).

The two groups were comparable, the randomization was successful (Table 12-13).

Comparing the levels (two groups pooled) there was no difference found regarding haemoglobin (p_{KW}=0.3721), parasite density (p_{KW}=0.4115). But there was a difference between the levels regarding methaemoglobin (p_{KW}<0.0001) with a higher mean in the first level (level 1: 1.5 g/dl, level 2: 1.1 g/dl, level 3: 1.1 g/dl). The descriptive statistics were presented by level in Table 12-10 for level 1 Table 12-11 for level 2 and Table 12-12 for level 3.

7.6 Analysis of the primary endpoint

The analysis of the primary endpoint is based on the FAS (and as sensitivity analysis on the PP set).

First primary endpoint, incidence of *relevant* adverse events (RAE): In the FAS in level 1 no RAE occurred, in level 2 in each group one RAE occurred, and in level 3 one RAE occurred in the 4x-daily-group, see Table 12-59 to Table 12-62. The summary in Table 7-2 shows, that all upper confidence limit were lower than the a priori specified 10% margin. In all cases the hypotheses could be rejected. Therefore it is shown that in all groups and levels the incidence rate of RAE *is* lower than 10% under the α-level of 5%. Narratives are given in section 7.7.9.

Table 7-2: Number of RAEs with one-sided CI by analysis population, group, and level

Analysis set	level	Statistic	2x daily	4x daily	Total
FAS	1	events/N (%)	0/72 (0.0%)	0/75 (0.0%)	0/147 (0.0%)
		exact 95% CI	[0%, 4.99%]	[0%, 4.80%]	[0%, 2.48%]
	2	events/N (%)	1/72 (1.4%)	1/78 (1.3%)	2/150 (1.3%)
		exact 95% CI	[0%, 6.42%]	[0%, 5.94%]	[0%, 4.14%]
	3	events/N (%)	0/53 (0.0%)	1/62 (1.6%)	1/115 (0.9%)
		exact 95% CI	[0%, 6.72%]	[0%, 7.42%]	[0%, 4.06%]
	Total	events/N (%)	1/197 (0.5%)	2/215 (0.9%)	3/412 (0.7%)
		exact 95% CI	[0%, 2.39%]	[0%, 2.90%]	[0%, 1.87%]
PP	1	events/N (%)	0/62 (0.0%)	0/66 (0.0%)	0/128 (0.0%)
		exact 95% CI	[0%, 5.78%]	[0%, 5.44%]	[0%, 2.84%]
	2	events/N (%)	0/64 (0.0%)	0/73 (0.0%)	0/137 (0.0%)
		exact 95% CI	[0%, 5.60%]	[0%, 4.93%]	[0%, 2.66%]
	3	events/N (%)	0/47 (0.0%)	1/52 (1.9%)	1/99 (1.0%)
		exact 95% CI	[0%, 7.55%]	[0%, 8.80%]	[0%, 4.70%]
	Total	events/N (%)	0/173 (0.0%)	1/191 (0.5%)	1/364 (0.3%)
		exact 95% CI	[0%, 2.11%]	[0%, 2.46%]	[0%, 1.30%]
PP *	1	events/N (%)	0/45 (0.0%)	0/47 (0.0%)	0/92 (0.0%)
		exact 95% CI	[0%, 7.87%]	[0%, 7.55%]	[0%, 3.93%]
	2	events/N (%)	0/64 (0.0%)	0/73 (0.0%)	0/137 (0.0%)
		exact 95% CI	[0%, 5.60%]	[0%, 4.93%]	[0%, 2.66%]
	3	events/N (%)	0/47 (0.0%)	1/52 (1.9%)	1/99 (1.0%)
		exact 95% CI	[0%, 7.55%]	[0%, 8.80%]	[0%, 4.70%]
	Total	events/N (%)	0/156 (0.0%)	1/172 (0.6%)	1/328 (0.3%)
		exact 95% CI	[0%, 2.34%]	[0%, 2.73%]	[0%, 1.44%]

* PP in the strong sense

Sensitivity analysis based on PP: The PP analysis comes to the same conclusion as the analysis based on the FAS with ITT principles.

Second primary endpoint, incidence of treatment failures (TF): In the FAS 84/412 treatment failures were counted. In all cases the upper bound of the one-sided 95% confidence interval was larger than

the a priori specified 15% margin, see Table 7-3. In none of the cases the hypotheses could be rejected on the 5% α-level.

Table 7-3: Number of TF with one-sided CI by analysis population, group, and level

Analysis set	level	statistic	2x daily	4x daily	Total
FAS	1	events/N (%)	15/72 (20.8%)	13/75 (17.3%)	28/147 (19.0%)
		exact 95% CI	[0%, 30.25%]	[0%, 26.14%]	[0%, 25.17%]
	2	events/N (%)	13/72 (18.1%)	18/78 (23.1%)	31/150 (20.7%)
		exact 95% CI	[0%, 27.17%]	[0%, 32.28%]	[0%, 26.86%]
	3	events/N (%)	11/53 (20.8%)	14/62 (22.6%)	25/115 (21.7%)
		exact 95% CI	[0%, 32.01%]	[0%, 33.03%]	[0%, 29.02%]
	Total	events/N (%)	39/197 (19.8%)	45/215 (20.9%)	84/412 (20.4%)
		exact 95% CI	[0%, 25.05%]	[0%, 26.02%]	[0%, 23.93%]
PP	1	events/N (%)	6/62 (9.7%)	4/66 (6.1%)	10/128 (7.8%)
		exact 95% CI	[0%, 18.21%]	[0%, 13.33%]	[0%, 12.89%]
	2	events/N (%)	5/64 (7.8%)	13/73 (17.8%)	18/137 (13.1%)
		exact 95% CI	[0%, 15.73%]	[0%, 26.81%]	[0%, 18.86%]
	3	events/N (%)	5/47 (10.6%)	5/52 (9.6%)	10/99 (10.1%)
		exact 95% CI	[0%, 21.08%]	[0%, 19.16%]	[0%, 16.53%]
	Total	events/N (%)	16/173 (9.2%)	22/191 (11.5%)	38/364 (10.4%)
		exact 95% CI	[0%, 13.71%]	[0%, 16.04%]	[0%, 13.46%]
PP *	1	events/N (%)	4/45 (8.9%)	3/47 (6.4%)	7/92 (7.6%)
		exact 95% CI	[0%, 19.20%]	[0%, 15.68%]	[0%, 13.82%]
	2	events/N (%)	5/64 (7.8%)	13/73 (17.8%)	18/137 (13.1%)
		exact 95% CI	[0%, 15.73%]	[0%, 26.81%]	[0%, 18.86%]
	3	events/N (%)	5/47 (10.6%)	5/52 (9.6%)	10/99 (10.1%)
		exact 95% CI	[0%, 21.08%]	[0%, 19.16%]	[0%, 16.53%]
	Total	events/N (%)	14/156 (9.0%)	21/172 (12.2%)	35/328 (10.7%)
		exact 95% CI	[0%, 13.67%]	[0%, 17.10%]	[0%, 13.90%]

* PP in the strong sense

Sensitivity analysis based on PP: The PP analysis where patients with missing information were eliminated instead of counted as failures the rates are lower. In all but one group*level

combinations the upper bound of the confidence interval is larger than 15%, only for level 1 in the 4x-daily-group the upper bound is 13.33%.

7.7 Secondary endpoint analyses

7.7.1 Incidence of early treatment failure (ETF)

In the FAS (PP set) [PP set in the strong sense] there were 29/412=7.0% (10/364=2.7%) [9/328=2.7%] ETF, see Table 12-84 and Table 12-71 (Table 12-75). In a linear model there was neither a group effect p_{LR}=0.9836 (p_{LR}=0.2484) [p_{LR}=0.3734] nor a linear level effect p_{LR}=0.1594 (p_{LR}=0.3565) [p_{LR}=0.3236] (interaction eliminated in all cases). Considered level as a factor a clear difference between level could be found in the PP set in this trial, FAS: p_{LR}=0.1701 (PP set: p_{LR}=0.0196) [PP set in the strong sense: p_{LR}=0.0192] with 2.3% for level 1, 5.1% in level 2 and 0% in level 3 in the PP set. However, this result is based on pretty sparse data. The main reasons for being a ETF were 12 times due to missing information and 5 times due to fever(>=37,5°C) on D3 (WHO) and parasite count > 0.

7.7.2 Incidence of late clinical failures (LCF)

In the FAS (PP set) [PP set in the strong sense] there were 55/412=13.3% (28/364=7.7%) [26/328=7.9%] LCF after 14 days, see Table 12-71 (Table 12-75). The main reasons for being LCF were 28 times due to fever(>=37,5°C) and parasite count>0 on D4-D14 (WHO) and 22 times due to missing information.

7.7.3 Incidence of treatment failures (TF)

The incidence of treatment failures was already discussed in the primary analysis, but only by group and level, no group and/or level comparison was done so far but mentioned here.

In the FAS (PP set) [PP set in the strong sense] there were 84/412=20.4% (38/364=10.4%) [35/328=10.7%] TF after 14 days, see Table 7-3, Table 12-85 and Table 12-71 (Table 12-75). In a linear model there is neither a group effect p_{LR}=0.7847 (p_{LR}=0.4814) [p_{LR}=0.3439] nor a level effect p_{LR}=0.5917 (p_{LR}=0.5129) [p_{LR}=0.6032] could be found in this trial (interaction eliminated in all cases, level was modelled linear). Considered level as a factor: p_{LR}=0.8636 (p_{LR}=0.3666) [p_{LR}=0.4042] the same conclusion could be drawn.

In the FAS (PP set) [PP set in the strong sense] there were 32/115=27.8% (16/99=16.2%) [16/99=16.2%] TF after 28 days at level 3 (not captured for level 1 and 2), see Table 12-71 (Table 12-75). The rates are roughly 5%-points higher than for the TF after 14 days.

7.7.4 Incidence of late parasitological failures (LPF)

In the FAS (PP set) [PP set in the strong sense] there were 87/412=21.1% (86/364=23.6%) [79/328=24.1%] LPF after 14 days, see Table 12-71 (Table 12-75). The main reason for being LCF was due to Temperature < 37,5°C on D14(WHO) and parasitaemia > 0.

7.7.5 Incidence of late parasitological failures (CPF)

The analysis of CPF (=ETF+LCF+LPF=1-ACPR) not originally mentioned in the trial protocol but was added post hoc.

In the FAS (PP set) [PP set in the strong sense] there were 166/412=40.3% (124/364=34.1%) [114/328=34.8%] CPF after 14 days, see Table 12-86. In a linear model there is neither a group effect p_{LR}=0.1718 (p_{LR}=0.2621) [p_{LR}=0.3822] nor a level effect p_{LR}=0.6002 (p_{LR}=0.9940) [p_{LR}=0.7182] could be found in this trial (interaction eliminated in all cases, level was modelled linear). Considered level as a factor: p_{LR}=0.3587 (p_{LR}=0.2396) [p_{LR}=0.3013] the same conclusion could be drawn.

In the FAS (PP set) [PP set in the strong sense] there were 76/115=66.1% (60/99=60.6%) [60/99=60.6%] CPF after 28 days for level 3 (not captured at level 1 and 2), see Table 12-88.

Table 7-4: Overview of efficacy parameters after 14 days by level (PP)

	Level 1 (N=128)	Level 2 (N=137)	Level 3 (N=99)	Total (N=364)
- ETF	3 (2.3%)	7 (5.1%)	0 (0.0%)	10 (2.7%)
- LCF	7 (5.5%)	11 (8.0%)	10 (10.1%)	28 (7.7%)
- LPF	30 (23.4%)	36 (26.3%)	20 (20.2%)	86 (23.6%)
- ACPR	88 (68.8%)	83 (60.6%)	69 (69.7%)	240 (65.9%)
- TF (ETF or LCF)	10 (7.8%)	18 (13.1%)	10 (10.1%)	38 (10.4%)
- CPF (TF or LPF)	40 (31.3%)	54 (39.4%)	30 (30.3%)	124 (34.1%)

7.7.6 Fever clearance time

There is no group*level interaction (time to event analysis). Modeling group and level no group effect can be found (FAS: p_{Cox}=0.7863; PP: p_{Cox}=0.8615) but a strong level effect (FAS: p_{Cox}<0.0001; PP: p_{Cox}<0.0001) with a shorter median fever clearance time in the third dose group (Table 7-5). Fever measurements were not taken by night, the corresponding Kaplan-Meier curve has therefore some steps (Figure 7-3).

Table 7-5: Median fever clearance time and 95% confidence intervals

Analysis set	level	2x daily	4x daily	Total
FAS	1	6.00 [5.47, 10.50]	5.83 [5.30, 6.58]	5.88 [5.55, 6.92]
	2	5.34 [4.12, 5.85]	5.40 [2.17, 6.22]	5.37 [4.62, 5.82]
	3	4.38 [1.55, 5.95]	1.85 [1.37, 5.73]	2.10 [1.55, 5.70]
	Total	5.55 [5.27, 5.85]	5.57 [5.08, 5.88]	5.55 [5.30, 5.78]
PP	1	5.89 [5.47, 10.50]	5.83 [5.23, 6.82]	5.83 [5.48, 6.82]
	2	5.31 [4.12, 5.80]	5.28 [1.52, 6.22]	5.30 [4.45, 5.70]
	3	1.88 [1.52, 5.72]	1.58 [1.23, 5.73]	1.82 [1.45, 5.70]
	Total	5.48 [4.80, 5.78]	5.42 [4.72, 5.88]	5.46 [5.15, 5.73]
PP*	1	5.80 [5.40, 10.37]	5.62 [4.93, 6.82]	5.79 [5.40, 6.82]
	2	5.31 [4.12, 5.80]	5.28 [1.52, 6.22]	5.30 [4.45, 5.70]
	3	1.88 [1.52, 5.72]	1.58 [1.23, 5.73]	1.82 [1.45, 5.70]
	Total	5.43 [4.58, 5.77]	5.35 [4.42, 5.82]	5.40 [4.72, 5.70]

* PP set in the strong sense

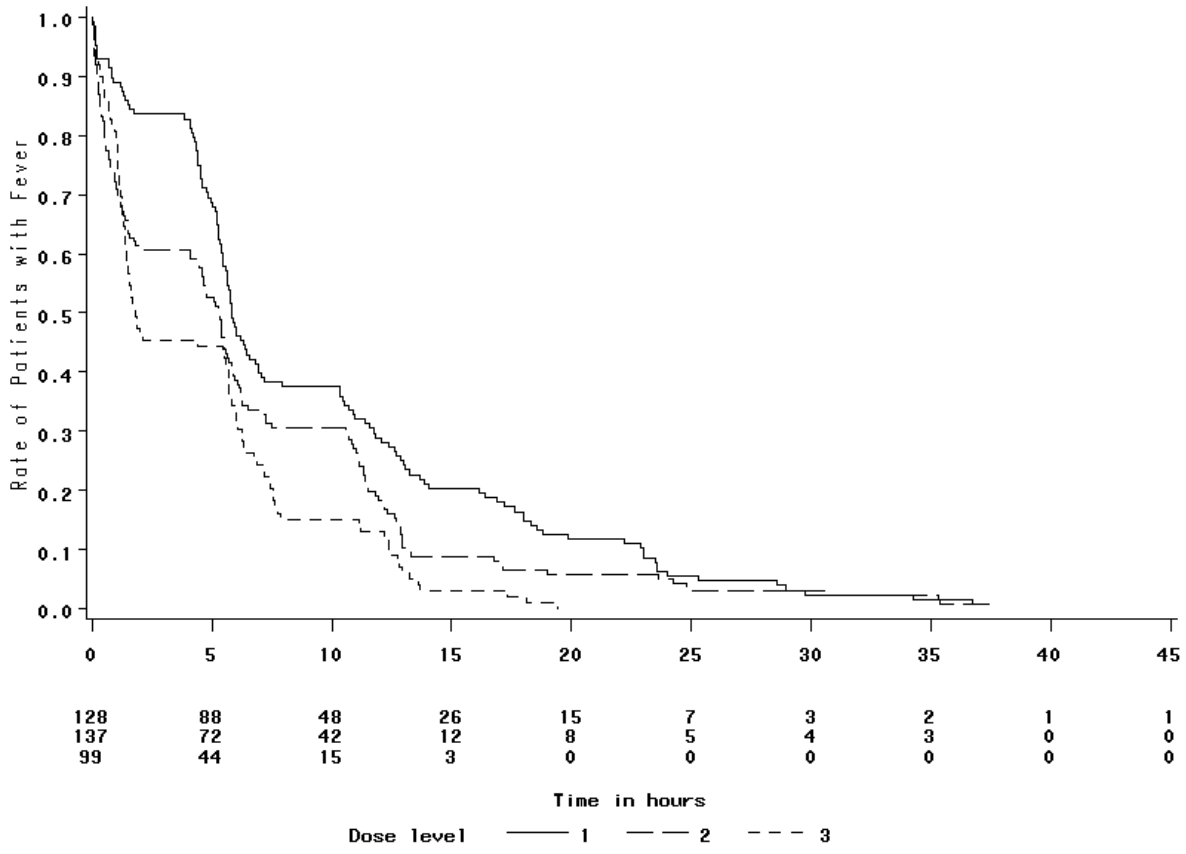

Figure 7-3: Kaplan-Meier curve for fever clearance by dose level (PP)

The fever measurements are summarised in the tables Table 12-36 to Table 12-53 and the intake of antipyretics is shown in chapter 7.7.12, further information about the clearance is given in Table 12-89 and Table 12-90.

7.7.7 Parasite clearance time

There is no group*level interaction (time to event analysis). Modeling group and level no group effect can be found (FAS: p_{Cox}=0.3247; PP: p_{Cox}=0.2647) and no level effect (FAS: p_{Cox}=0.6857; PP: p_{Cox}=0.2387) with a shorter median fever clearance time in the third dose group (Table 7-6). Blood measurements were only taken once per day, the corresponding Kaplan-Meier curve has therefore some steps (Figure 7-4).

Further information about the clearance is given in Table 12-91, Table 12-92, and Table 12-93.

Table 7-6: Median parasite clearance time and 95% confidence intervals

Analysis set	level	2x daily	4x daily	Total
FAS	1	67.57 [66.57, 68.42]	68.10 [67.68, 68.43]	67.93 [67.03, 68.33]
	2	68.13 [67.67, 68.95]	67.77 [67.32, 68.68]	68.00 [67.62, 68.68]
	3	69.02 [68.27, 69.43]	68.10 [67.48, 68.68]	68.40 [68.08, 68.87]
	Total	68.27 [67.82, 68.75]	68.03 [67.68, 68.33]	68.10 [67.87, 68.40]
PP	1	67.50 [66.55, 68.28]	67.98 [67.03, 68.42]	67.80 [67.02, 68.28]
	2	68.23 [67.67, 69.02]	67.77 [67.25, 68.70]	67.98 [67.58, 68.70]
	3	69.02 [68.40, 69.43]	68.10 [67.48, 68.87]	68.53 [68.05, 69.05]
	Total	68.25 [67.78, 68.80]	68.00 [67.62, 68.33]	68.07 [67.82, 68.40]
PP*	1	67.02 [66.22, 68.28]	68.00 [66.97, 68.57]	67.57 [66.93, 68.40]
	2	68.23 [67.67, 69.02]	67.77 [67.25, 68.70]	67.98 [67.58, 68.70]
	3	69.02 [68.40, 69.43]	68.10 [67.48, 68.87]	68.53 [68.05, 69.05]
	Total	68.31 [67.78, 68.90]	68.00 [67.57, 68.42]	68.09 [67.82, 68.47]

* PP set in the strong sense

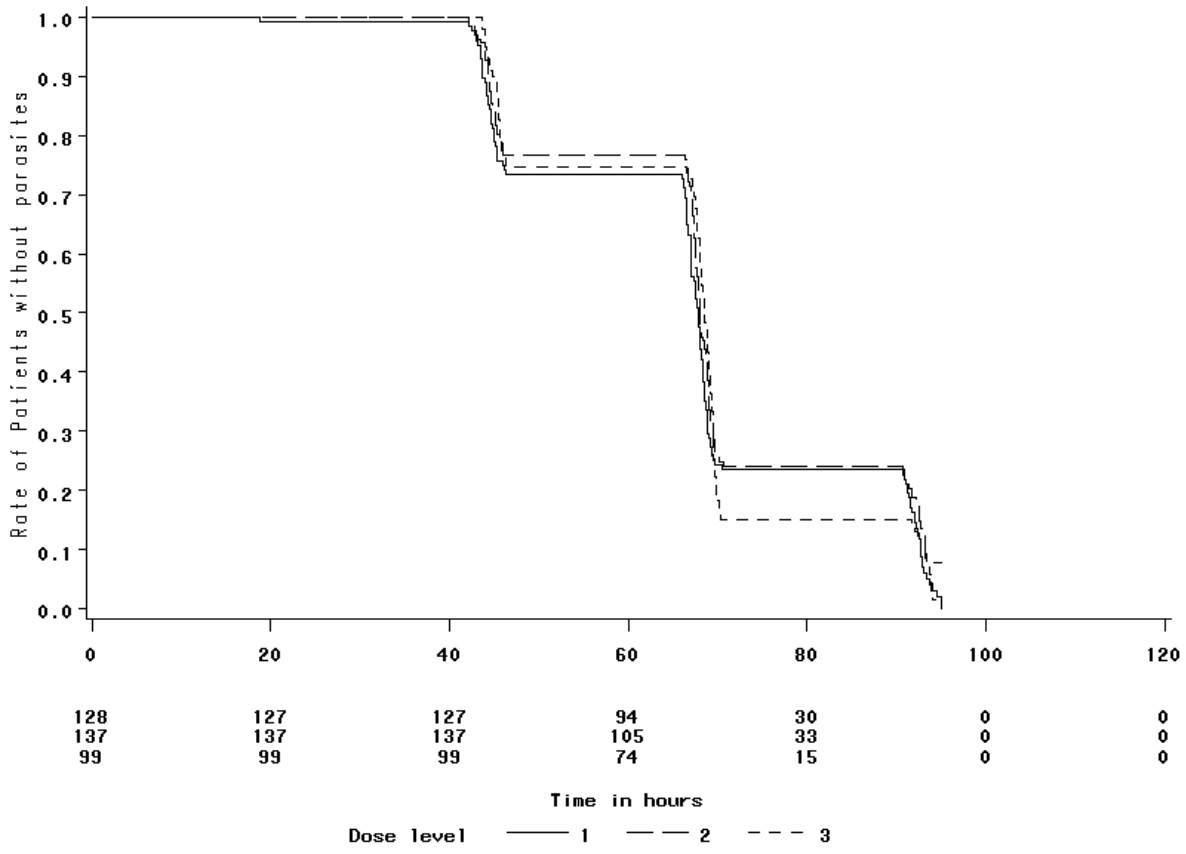

Figure 7-4: Kaplan-Meier curve for parasite clearance by dose level (PP)

7.7.8 Change in haemoglobin after 4 (or 7) and 14 days compared to baseline

This analysis is based on FAS: There was no Hb measurement done for the third dose level after 14 days due to administrative reasons. However, for all three levels there was no difference regarding the Hb changes between the groups (2x daily versus 4x daily), see Table 12-18 and Table 12-24 for level 1, Table 12-19 and Table 12-25 for level 2, Table 12-20 and Table 12-26 for level 3. When using the our understanding of the WHO definition the start of treatment is considered as the start of the first day rather than the calendar day; those data can be found in Table 12-21 and Table 12-33 for level 1, Table 12-22 and Table 12-34 for level 2, and Table 12-23 and Table 12-35 for level 3. The interpretation of the data is comparable.

In all three levels (pooled the two groups) a significant decrease of the Hb measurement was found after 4 days and in all two levels still a significant decrease of the Hb measurement was found after 14 days (level 1: p_{WSR}=0.0322, level 2: p_{WSR}=0.0041, see Table 12-30 and Table 12-31), but the decrease is smaller than after 4 days and not significant without pooling the data (lower power).

The time between baseline measurement and day 4 (day 14) measurement was 70.2+/–1.1 hours (312.1+/–7.8 hours) or 2.92+/–0.05 days (13.01+/–0.33 days). A difference in the change of Hb from baseline to day 4 between the levels (p_F=0.1068) and groups (2x versus 4x) (p_F=0.3967) cannot be shown (parametric linear model, F-Test, type III, level as linear covariate, interaction term eliminated). A difference in the change of Hb from baseline to day 14 between the levels (level 1 versus level 2: p_F=0.5484) and groups (2x versus 4x: p_F=0.1453) cannot be shown (parametric linear model, F-Test, type III, interaction term eliminated).

When selecting the PP set or the PP set in the strong sense, there is also no difference between groups and levels regarding the decrease of Hb (data not shown).

Table 7-7: Haemoglobin and change of haemoglobin by group and level (FAS)

	level 1		level 2		level 3	
Characteristic	2x	4x	2x	4x	2x	4x
Haemoglobin[g/dl] at Baseline						
- N	72	75	72	78	53	62
- Mean +/- SD	9.7 +/- 1.1	9.7 +/- 1.1	9.5 +/- 1.0	9.7 +/- 1.2	9.6 +/- 0.9	9.4 +/- 0.8
- 95% CI mean	[9.43; 9.93]	[9.48; 9.99]	[9.28; 9.75]	[9.45; 9.98]	[9.36; 9.83]	[9.21; 9.63]
Haemoglobin[g/dl] at Day4						
- N	68	70	67	77	51	61
- Mean +/- SD	8.8 +/- 0.9	8.9 +/- 1.0	8.9 +/- 1.1	8.8 +/- 1.2	8.9 +/- 1.0	8.8 +/- 1.1
- 95% CI mean	[8.55; 9.01]	[8.69; 9.17]	[8.57; 9.14]	[8.47; 9.03]	[8.61; 9.17]	[8.55; 9.11]
Haemoglobin[g/dl] at Day14 $						
- N	67	70	64	73	-	-
- Mean +/- SD	9.4 +/- 1.0	9.5 +/- 1.2	9.4 +/- 0.9	9.3 +/- 1.1	-	-
- 95% CI mean	[9.20; 9.68]	[9.24; 9.82]	[9.20; 9.68]	[9.02; 9.53]	-	-
Change in Haemoglobin[g/dl] Day4-Baseline						
- N	68	70	67	77	51	61
- Mean +/- SD	-0.8 +/- 0.7	-0.8 +/- 0.9	-0.7 +/- 0.9	-1.0 +/- 1.0	-0.7 +/- 0.8	-0.6 +/- 0.9
- 95% CI mean	[-1.0; -0.7]	[-1.0; -0.6]	[-0.9; -0.4]	[-1.2; -0.7]	[-0.9; -0.5]	[-0.8; -0.4]
- p-value *	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Change in Haemoglobin[g/dl] Day14-Baseline $						
- N	67	70	64	73	-	-
- Mean +/- SD	-0.2 +/- 1.0	-0.2 +/- 1.3	-0.1 +/- 1.0	-0.5 +/- 1.2	-	-
- 95% CI mean	[-0.4; 0.0]	[-0.5; 0.1]	[-0.3; 0.1]	[-0.7; -0.2]	-	-
- p-value *	0.1058	0.1651	0.3081	0.0029	-	-

$ including data from days 12-16, * Wilcoxon-Sign-Rank Test

7.7.9 Incidence of observed serious adverse events

There were 3 in 412 (0.7%, one-sided 95% CI [0%, 1.87%], two-sided 95% CI [0.15%, 2.11%) patients with serious adverse events (Table 7-8 and Table 12-95). All SAEs were also RAEs and vice versa. In the following narratives of the three patients are presented.

One 13 months old girl (No. 203, G6PD sufficient, body weight = 7kg, group = 4x daily, level = 2), included, randomized and first treated on the 24. Aug 2004 had “Diarrhée(Gastro-enterite fébrile)” (MedDRA preferred term: Diarrhoea), started on the 25. Aug 2004, stopped on the 31 Aug 2004. She was late clinical failure. The SAE was rated as “possibly related” and treated with Paracetamol, Debridat, Cefadroxil (Oracefal), Metronidazol. This SAE was rated as RAE due to “Study drug related SAE”.

One 53 months old boy (No. 312, G6PD sufficient, body weight = 16kg, group = 2x daily, level = 2), included, randomized and first treated on the 17. Sept 2004 had “Paludisme grave” (MedDRA preferred term: Cerebral malaria), started on the 18. Sept 2004, stopped on the 20. Sept 2004. He was early treatment failure. The SAE was rated as “unrelated” and treated with Ceftriaxon, Gentamycin, Sulfadoxa/Pyrimethamin (Fansidar). This SAE was rated as RAE due to “Severe neurological disorders”.

One 28 months old boy (No. 461, G6PD homozygote deficient, body weight = 13kg, group = 4x daily, level = 3), included, randomized and first treated on the 12. Oct 2004 had “Anemie grave Hb 4,7” (MedDRA preferred term: Anaemia), started on the 15. Oct 2004, stopped on the 27. Oct 2004. Clinically there were no signs of haemolysis and total serum bilirubin was normal on day 3. His Hb was 8.7 g/dl at baseline 8.6 g/dl on the 27. Oct 2004. He was late clinical failure. The SAE was rated as “possibly related”and treated with Ceftriaxon and Iron. This SAE was rated as RAE due to “Acute haemolysis”.

Table 7-8: Serious adverse events (FAS)

Level		2x daily	4x daily	Total
1	Num. of Pat. with ≥1 SAE	0/72 (0%)	0/75 (0%)	0/147 (0%)
	Num. of SAE	0	0	.
2	Num. of Pat. with ≥1 SAE	1/72 (1.4%)	1/78 (1.3%)	2/150 (1.3%)
	Num. of SAE	1	1	2
3	Num. of Pat. with ≥1 SAE	0/53 (0%)	1/62 (1.6%)	1/115 (0.9%)
	Num. of SAE	0	1	1
Total	Num. of Pat. with ≥1 SAE	1/197 (0.5%)	2/215 (0.9%)	3/412 (0.7%)
	Num. of SAE	1	2	3

7.7.10 Incidence of observed and self-reported non-serious adverse events

Regarding AEs and non-serious AEs over the 14 days observation period no group difference can be found (Table 7-9), whereas less adverse events were reported in level 2 and 3. This may be due to an underreporting during the conduct of the clinical trial. However, no increase of adverse events can be seen with higher MB doses (Table 12-94).

Categorizing the AEs according to MedDRA using preferred terms (PT) (but also high-level-terms (HLT) or high-level-group-terms (HLGT)) showed (Table 12-99), that in this trial more children in the 2x daily group vomitted than in the 4x daily group (but higher dose per drug intake), see Table 12-96 to Table 12-107. On the other hand regarding diarrhoea the opposite was observed. No definite conclusion can be drawn due to sparse data.

Table 7-9: Overview of AEs and non-serious AEs by group and level (FAS)

Level		2x daily	4x daily	Total
1	Num. of Pat. with ≥1 AE	25/72 (34.7%)	23/75 (30.7%)	48/147 (32.7%)
	Num. of AE	30	27	57
2	Num. of Pat. with ≥1 AE	9/72 (12.5%)	12/78 (15.4%)	21/150 (14.0%)
	Num. of AE	9	12	21
3	Num. of Pat. with ≥1 AE	5/53 (9.4%)	10/62 (16.1%)	15/115 (13.0%)
	Num. of AE	7	11	18
Total	Num. of Pat. with ≥1 AE	39/197 (19.8%)	45/215 (20.9%)	84/412 (20.4%)
	Num. of AE	46	50	96
1	Num. of Pat. with ≥1 non-SAE	25/72 (34.7%)	23/75 (30.7%)	48/147 (32.7%)
	Num. of non-SAE	30	27	57
2	Num. of Pat. with ≥1 non-SAE	8/72 (11.1%)	11/78 (14.1%)	19/150 (12.7%)
	Num. of non-SAE	8	11	19
3	Num. of Pat. with ≥1 non-SAE	5/53 (9.4%)	10/62 (16.1%)	15/115 (13.0%)
	Num. of non-SAE	7	10	17
Total	Num. of Pat. with ≥1 non-SAE	38/197 (19.3%)	44/215 (20.5%)	82/412 (19.9%)
	Num. of non-SAE	45	48	93

7.7.11 Whole blood CQ and MB kinetics

The presentation of mean AUC, Cmax, Tmax, elimination half life is not part of this report.

7.7.12 Monitoring of concomitant drug intake

Table 12-54 to Table 12-57 show the given concomitant drug intake by medication group (antibiotics, antihistaminics, antimalarials, antipyretics, others). Table 7-10 gives the number of patients with medication (by medication group) for the PP population (see Table 12-58 for FAS). No difference can be seen between groups. No difference can be seen between levels for antibiotics, antihistaminics, and other medications whereas more antimalarials and less antipyretics were taken in level 3.

Table 7-10: Number of patients with concomitant medication by group and level (PP)

Medication	level	2x daily	4x daily	Total
Antibiotic	1	26/62 (41.9%)	21/66 (31.8%)	47/128 (36.7%)
	2	18/64 (28.1%)	23/73 (31.5%)	41/137 (29.9%)
	3	13/47 (27.7%)	23/52 (44.2%)	36/99 (36.4%)
	Total	57/173 (32.9%)	67/191 (35.1%)	124/364 (34.1%)
Antihistaminic	1	1/62 (1.6%)	1/66 (1.5%)	2/128 (1.6%)
	2	1/64 (1.6%)	3/73 (4.1%)	4/137 (2.9%)
	3	1/47 (2.1%)	2/52 (3.8%)	3/99 (3.0%)
	Total	3/173 (1.7%)	6/191 (3.1%)	9/364 (2.5%)
Antimalarial	1	23/62 (37.1%)	19/66 (28.8%)	42/128 (32.8%)
	2	27/64 (42.2%)	27/73 (37.0%)	54/137 (39.4%)
	3	24/47 (51.1%)	31/52 (59.6%)	55/99 (55.6%)
	Total	74/173 (42.8%)	77/191 (40.3%)	151/364 (41.5%)
Antipyretic	1	23/62 (37.1%)	25/66 (37.9%)	48/128 (37.5%)
	2	21/64 (32.8%)	37/73 (50.7%)	58/137 (42.3%)
	3	10/47 (21.3%)	15/52 (28.8%)	25/99 (25.3%)
	Total	54/173 (31.2%)	77/191 (40.3%)	131/364 (36.0%)
Other	1	29/62 (46.8%)	32/66 (48.5%)	61/128 (47.7%)
	2	35/64 (54.7%)	32/73 (43.8%)	67/137 (48.9%)
	3	25/47 (53.2%)	24/52 (46.2%)	49/99 (49.5%)
	Total	89/173 (51.4%)	88/191 (46.1%)	177/364 (48.6%)

7.7.13 G6PD assessment based on PCR

As presented in section 78.5% of the children were G6PD sufficient. In 8 children the Hb value dropped >3g/dl, 4 of these were found to be G6PD deficient (homozygote) and the other 4 were G6PD sufficient. Under the hypotheses of no relation between G6PD status and Hb drop >3g/dl about 2 (21.5%) children were expected to be G6PD deficient and 6 (78.5%) sufficient. But due to sparse data this hypothesis is difficult to investigate (p_{Fisher}=0.0693).

Table 7-11: G6PD status at baseline

	2x daily	4x daily	Total
G6PD status (PCR method)			p_{Chi}=0.4011
- sufficient	154 (78.6%)	167 (78.4%)	321 (78.5%)
- heterozygot deficient	27 (13.8%)	23 (10.8%)	50 (12.2%)
- homozygote deficient	15 (7.7%)	23 (10.8%)	38 (9.3%)
- Missing	1	2	3

8 DISCUSSION

Safety judgement: Safety for all three dose levels reached. No increase of adverse events can be seen with higher MB doses.

Efficacy judgment: So called efficacy was not shown in FAS, but the combination has the chance to reach the predefined margin: In the PP set the one-sided confidence interval for the whole population for the treatment failures was [0%, 13.5%] with a point estimate of 10.4%. But even 10% is still too high. In total the combination of MB and CQ seems to be effective.

Group comparison: 2x versus 4x: no difference could be found. This trial gives no reason for a dose regimen of 4x daily instead of 2x.

Level comparison: Starting from inhomogeneous baseline data between levels there were some difference between levels (quicker fever clearance time at level 3 with less children with antipyretics, more reported adverse events in level 1, more early treatment failures in level 2). However, focusing on the treatment failure after 14 days no level effect could be found. All level effects could be related to a time influence or other reasons of bias.

Conclusion: Our results demonstrate for the first time that MB, a cheap drug which is registered in most countries, is safe and could be effective in combination with CQ against malaria in SSA. To investigate the efficacy of MB a controlled trial with MB versus CQ-MB would be necessary. But, however, given the high background resistance in most SSA countries, CQ is no longer a good choice as a partner drug. MB has a short plasma half life (15 hours) and – in analogy to the artemisinin combination schemes – needs to be combined with a locally effective partner drug when given in a three day regimen (Greenwood et al. 2005). Further studies are needed to assess the importance of possible rare side effects such as haemolysis, to study simpler treatment regimens, and determine the full potential of MB in combination with other drugs in different SSA populations.

9 ACKNOWLEDGEMENTS

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11 APPENDIX: FIGURES

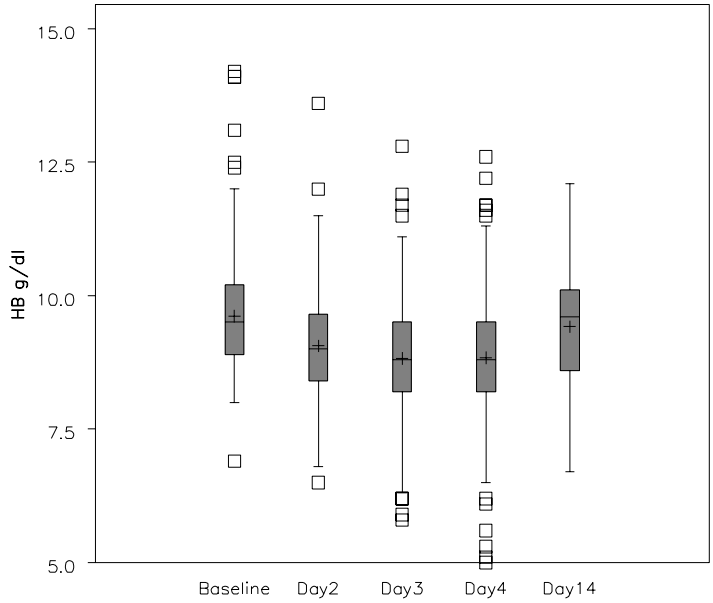


Figure 11-1: Haemoglobin over time of all patients (calendar days)

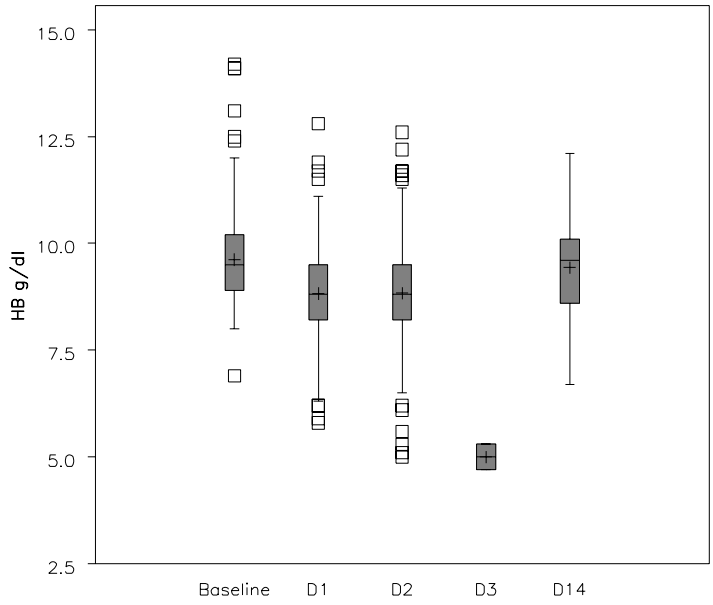
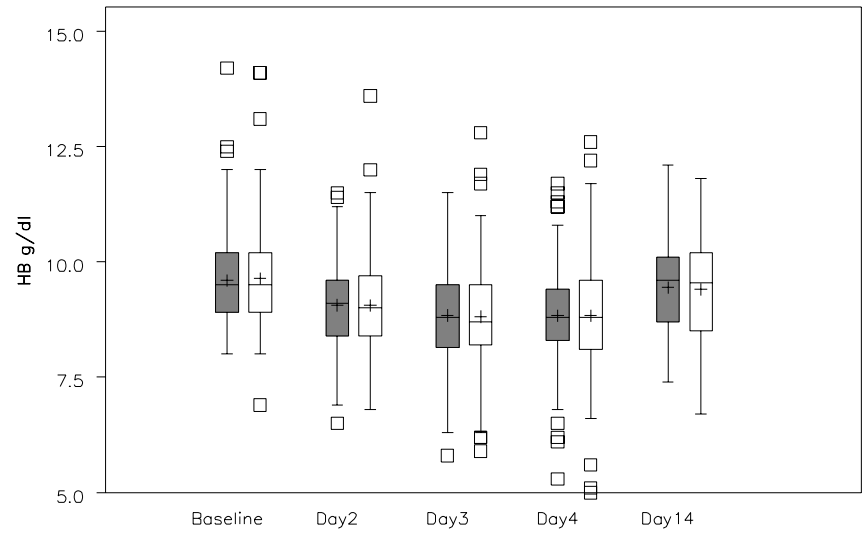
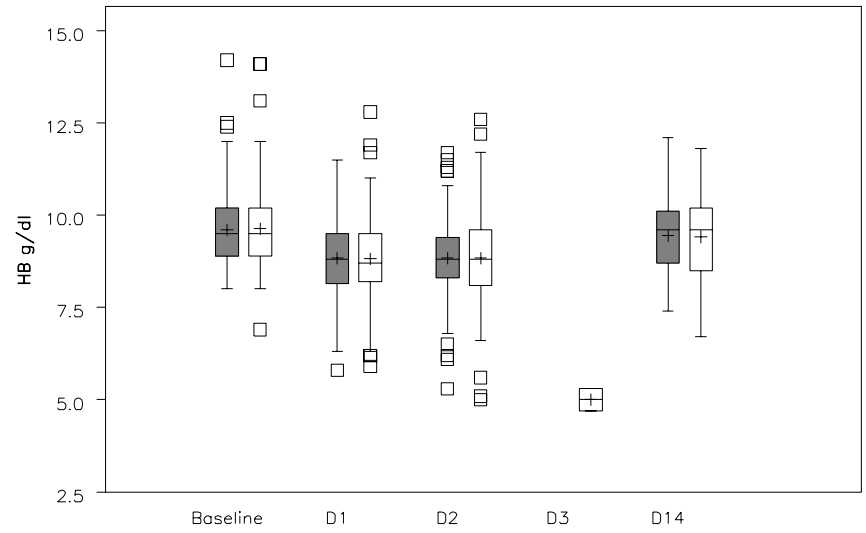


Figure 11-2: Haemoglobin over time of all patients (WHO days)



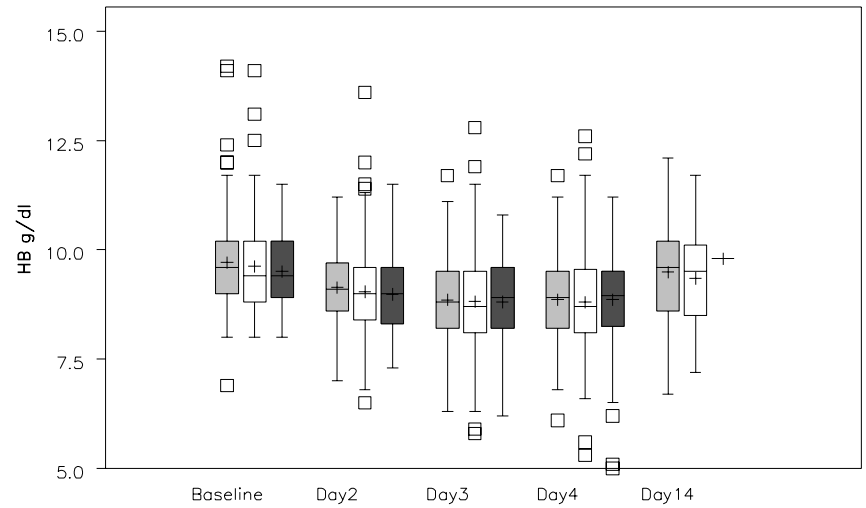
grey = 2x daily
white= 4x daily

Figure 11-3: Haemoglobin over time by group (calendar days)



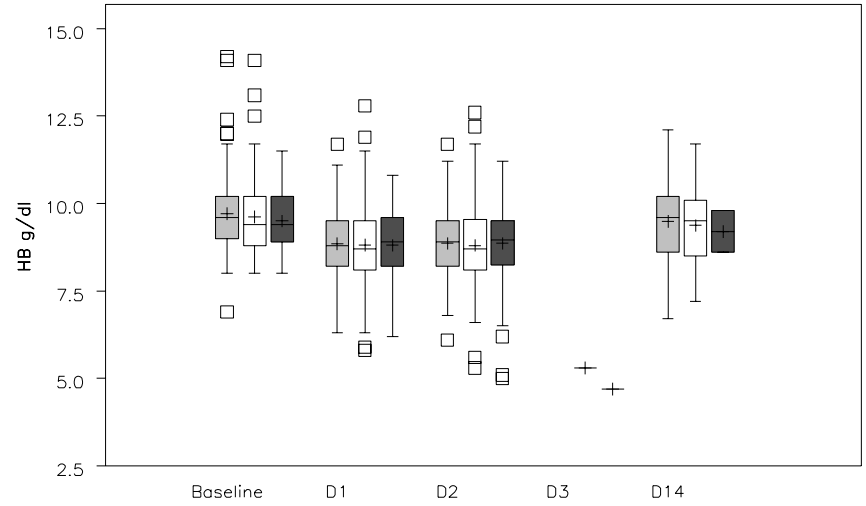
grey = 2x daily
white= 4x daily

Figure 11-4: Haemoglobin over time by group (WHO days)



grey = Level 1
white = Level 2
dark–grey = Level 3

Figure 11-5: Haemoglobin over time by level (calendar days)



grey = Level 1
white = Level 2
dark–grey = Level 3

Figure 11-6: Haemoglobin over time by level (WHO days)

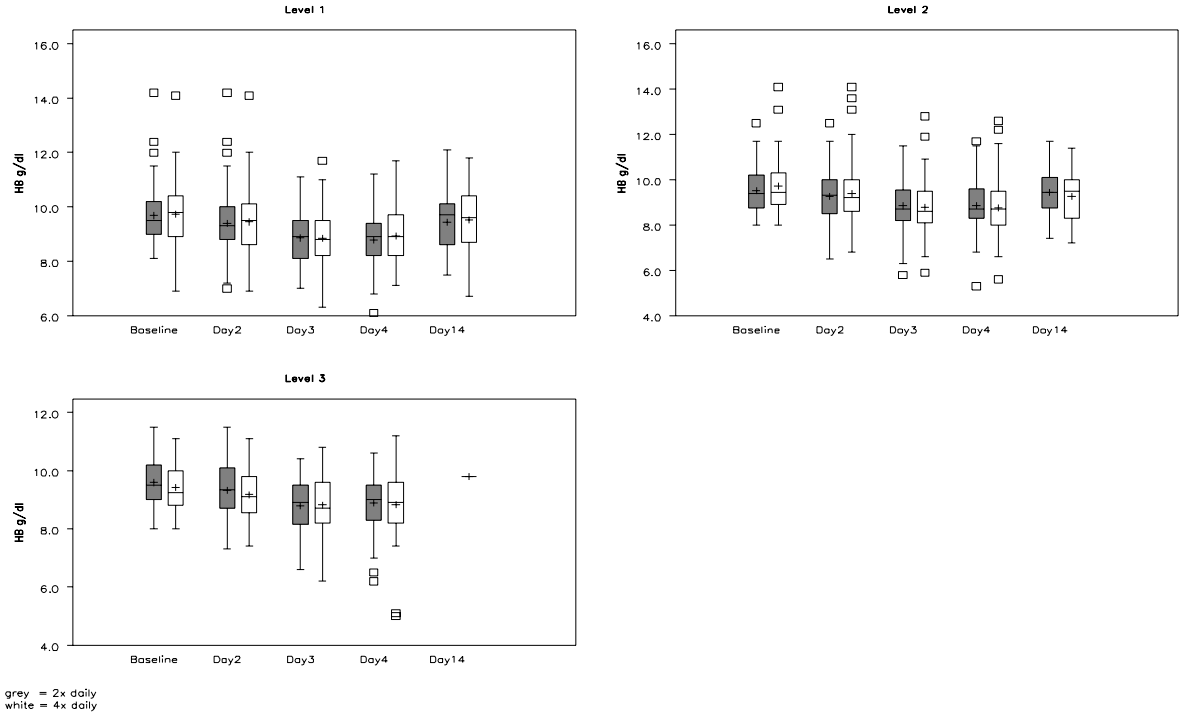


Figure 11-7: Haemoglobin over time by group and level (calendar days)

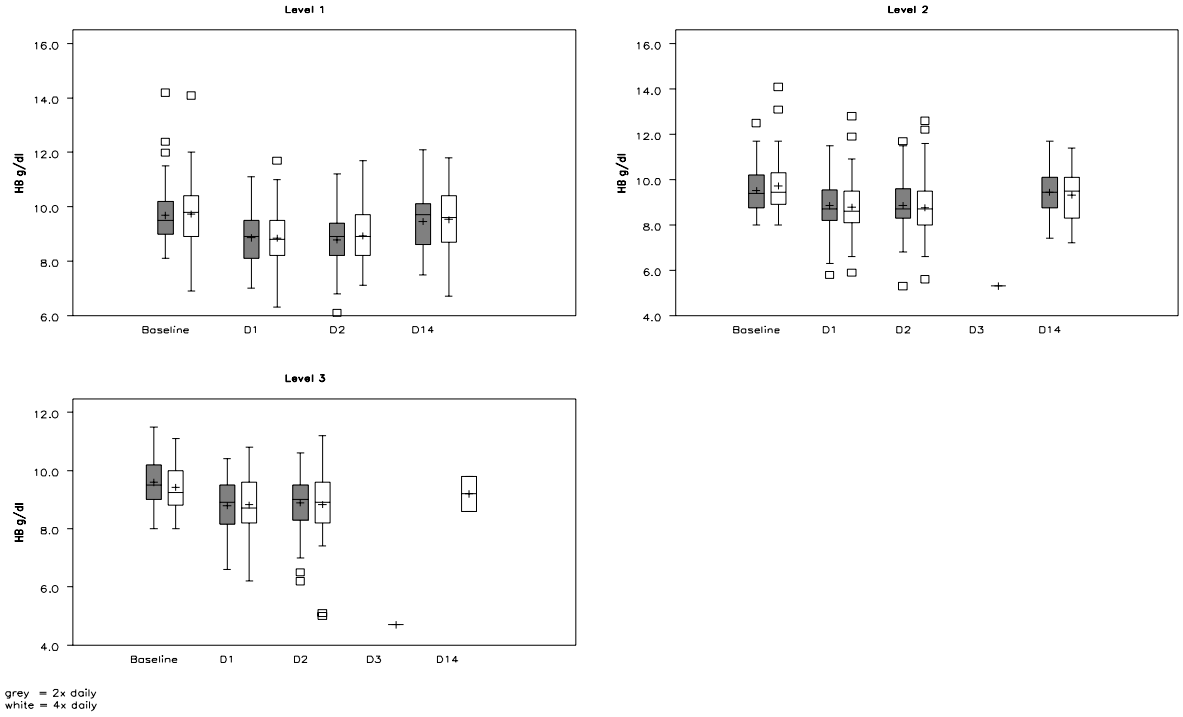


Figure 11-8: Haemoglobin over time by group and level (WHO days)

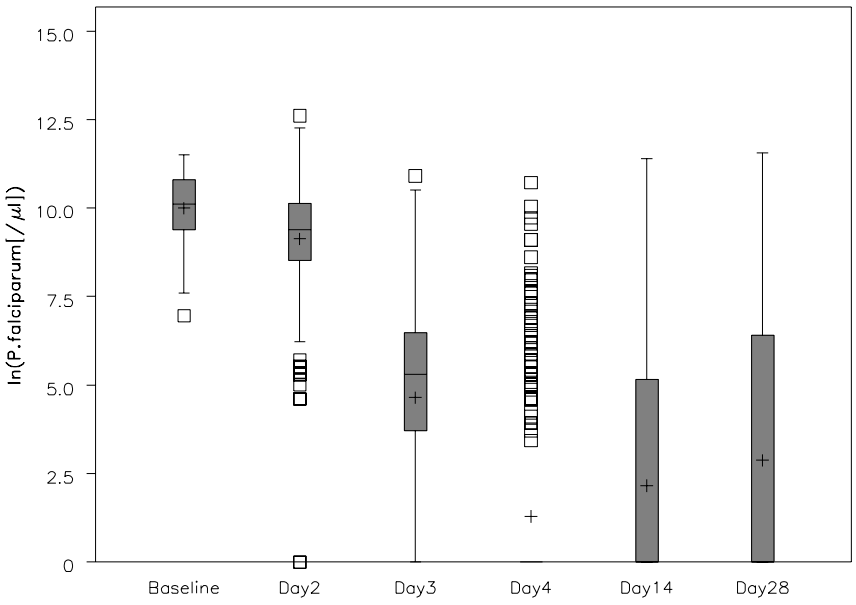


Figure 11-9: ln(parasite count) over time (calendar day)

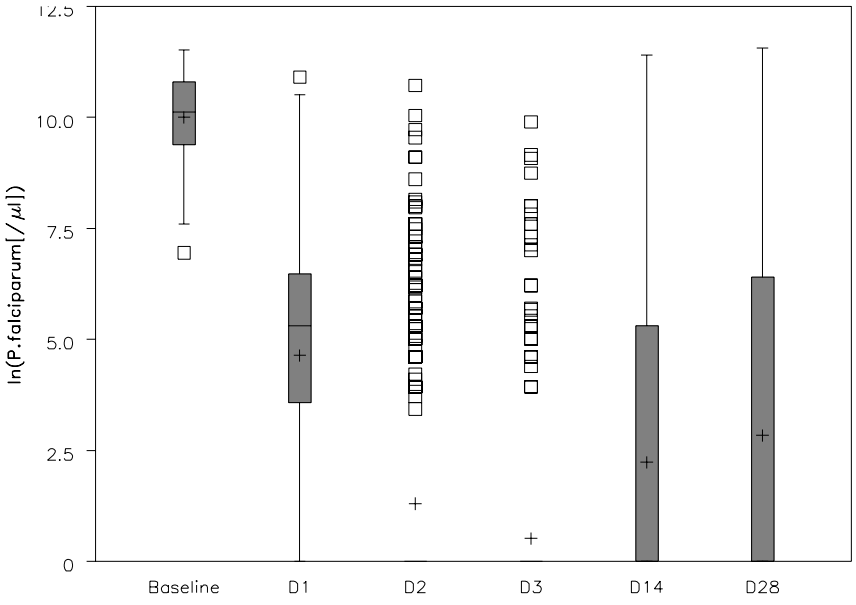
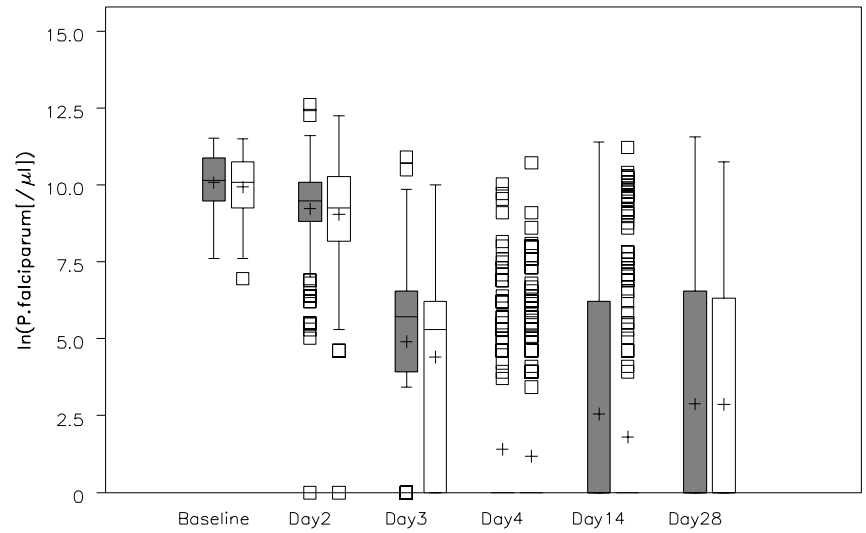
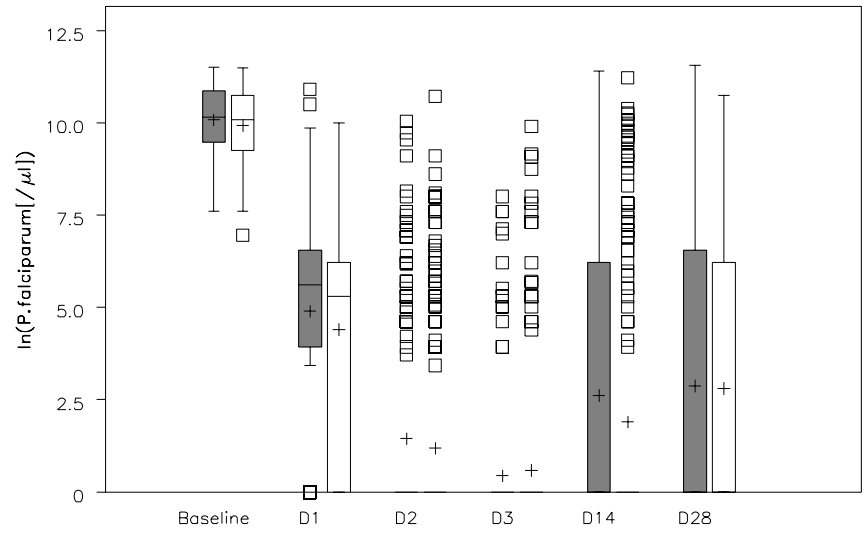


Figure 11-10: ln(parasite count) over time (WHO day)



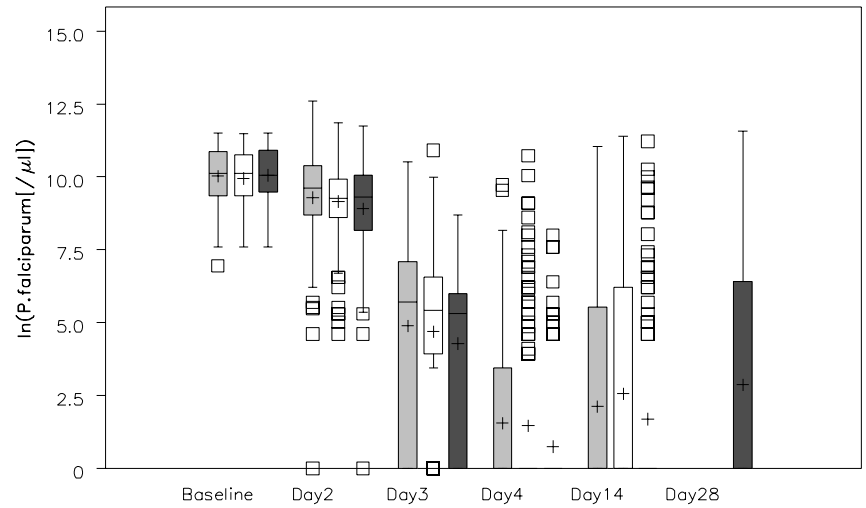
grey = 2x daily
white= 4x daily

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



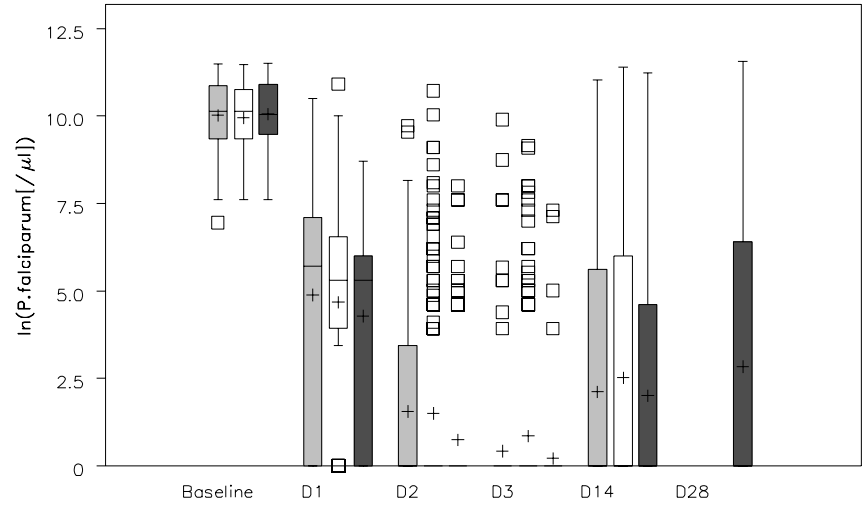
grey = 2x daily
white= 4x daily

Figure 11-12: ln(parasite count) over time by group (WHO day)



grey = Level 1
white = Level 2
dark–grey = Level 3

Figure 11-13: ln(parasite count) over time by level (calendar day)



grey = Level 1
white = Level 2
dark–grey = Level 3

Figure 11-14: ln(parasite count) over time by level (WHO day)

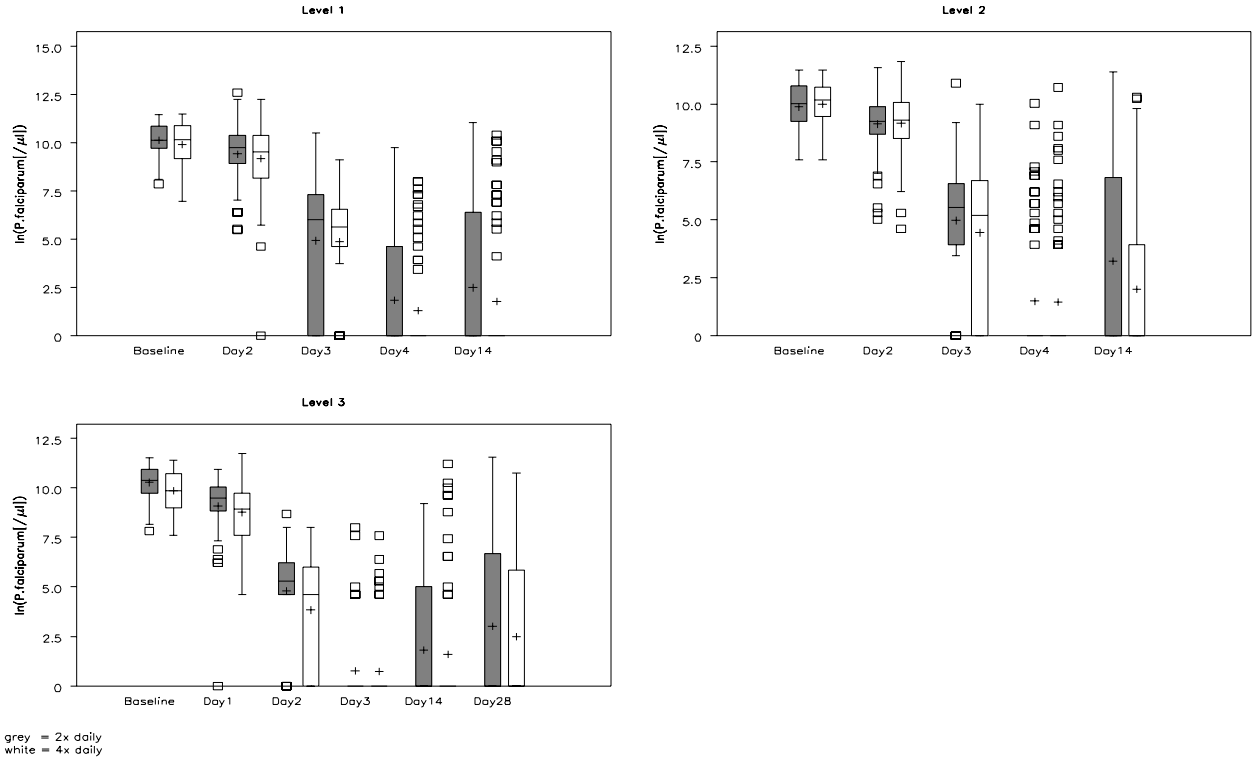


Figure 11-15: ln(parasite count) over time by group and level (calendar day)

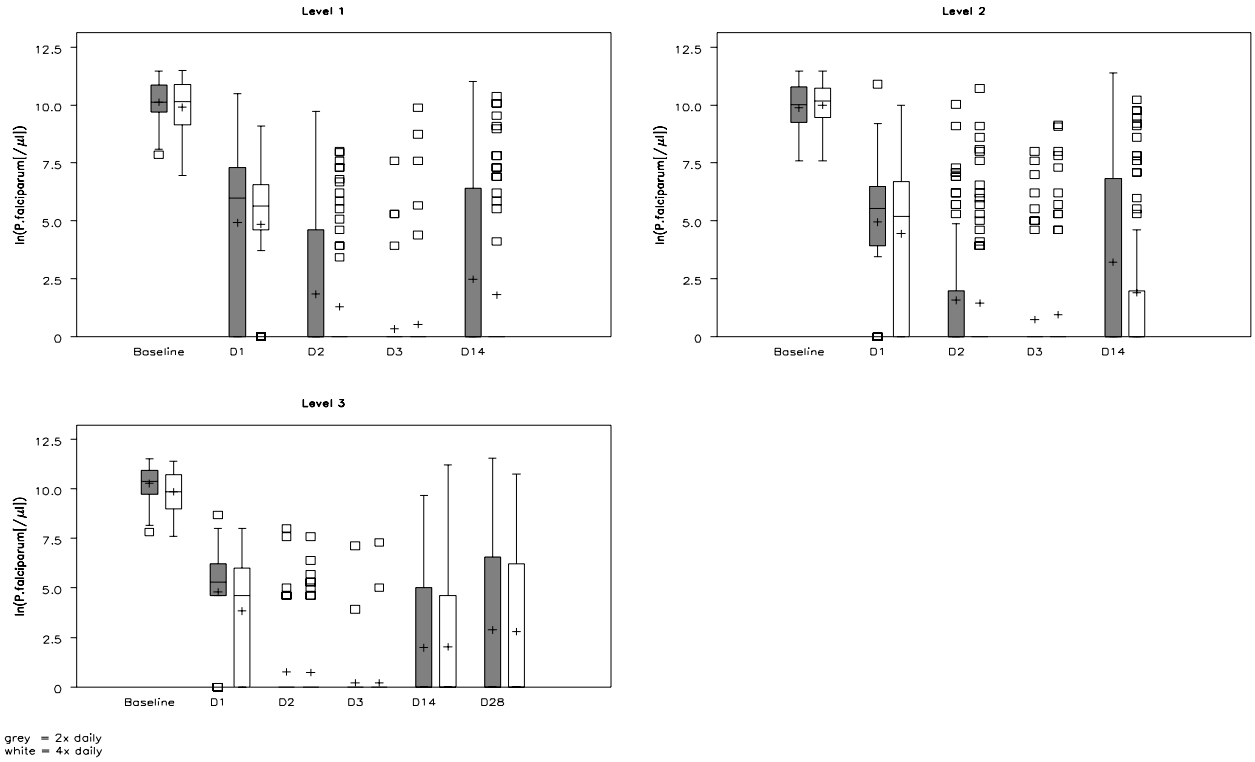


Figure 11-16: ln(parasite count) over time by group and level (WHO day)

12 APPENDIX: TABLES

Table 12-1: Recruiting of patients for all levels (FAS)

Week	from - to	N	N(%)cumulative
1	19/07/2004 - 25/07/2004	3	3(0.7%)
2	26/07/2004 - 01/08/2004	21	24(5.8%)
3	02/08/2004 - 08/08/2004	48	72(17.5%)
4	09/08/2004 - 15/08/2004	52	124(30.1%)
5	16/08/2004 - 22/08/2004	23	147(35.7%)
6	23/08/2004 - 29/08/2004	32	179(43.4%)
7	30/08/2004 - 05/09/2004	24	203(49.3%)
8	06/09/2004 - 12/09/2004	29	232(56.3%)
9	13/09/2004 - 19/09/2004	34	266(64.6%)
10	20/09/2004 - 26/09/2004	31	297(72.1%)
11	27/09/2004 - 03/10/2004	23	320(77.7%)
12	04/10/2004 - 10/10/2004	21	341(82.8%)
13	11/10/2004 - 17/10/2004	35	376(91.3%)
14	18/10/2004 - 24/10/2004	23	399(96.8%)
15	25/10/2004 - 31/10/2004	13	412(100.0%)

Table 12-2: Analysis sets and protocol compliance for Level 1

	2x daily N(%)	4x daily N(%)	Total N(%)
Included pat. (informed consent)	79(100.0%)	78(100.0%)	157(100.0%)
- Pat. without trial medication (Repeated vomiting)	7(8.9%)	3(3.8%)	10(6.4%)
- Pat. without trial medication (Other reason)	0(0.0%)	0(0.0%)	0(0.0%)
Pat. in FAS	72(91.1%)	75(96.2%)	147(93.6%)
- Pat. who vomited and the drug was not given again	3(3.8%)	4(5.1%)	7(4.5%)
- Pat. who vomited and it is unclear whether it was given again	0(0.0%)	0(0.0%)	0(0.0%)
- Pat. who violate inclusion/exclusion criteria	0(0.0%)	1(1.3%)	1(0.6%)
- Pat. without blue urine	0(0.0%)	0(0.0%)	0(0.0%)
- Withdrawal of informed consent	0(0.0%)	0(0.0%)	0(0.0%)
- Adverse event	0(0.0%)	0(0.0%)	0(0.0%)
- Investigators judgement	1(1.3%)	0(0.0%)	1(0.6%)
- Lost to follow up	0(0.0%)	0(0.0%)	0(0.0%)
- Death	0(0.0%)	0(0.0%)	0(0.0%)
- No Information on D14 given	4(5.1%)	1(1.3%)	5(3.2%)
- treated (D4-D13) with antimalarials although no fever and/or no parasites	2(2.5%)	3(3.8%)	5(3.2%)
Pat. in PP set	62(78.5%)	66(84.6%)	128(81.5%)
- Pat. who got the wrong concentration of MB	17(21.5%)	19(24.4%)	36(22.9%)
Pat. in PP set with correct concentraion of MB	45(57.0%)	47(60.3%)	92(58.6%)

% are based on all included patients

Table 12-3: Analysis sets and protocol compliance for Level 2

	2x daily N(%)	4x daily N(%)	Total N(%)
Included pat. (informed consent)	77(100.0%)	78(100.0%)	155(100.0%)
- Pat. without trial medication (Repeated vomiting)	2(2.6%)	0(0.0%)	2(1.3%)
- Pat. without trial medication (Other reason)	3(3.9%)	0(0.0%)	3(1.9%)
Pat. in FAS	72(93.5%)	78(100.0%)	150(96.8%)
- Pat. who vomited and the drug was not given again	3(3.9%)	0(0.0%)	3(1.9%)
- Pat. who vomited and it is unclear whether it was given again	0(0.0%)	0(0.0%)	0(0.0%)
- Pat. who violate inclusion/exclusion criteria	0(0.0%)	0(0.0%)	0(0.0%)
- Pat. without blue urine	0(0.0%)	0(0.0%)	0(0.0%)
- Withdrawal of informed consent	1(1.3%)	0(0.0%)	1(0.6%)
- Adverse event	1(1.3%)	0(0.0%)	1(0.6%)
- Investigators judgement	0(0.0%)	0(0.0%)	0(0.0%)
- Lost to follow up	3(3.9%)	2(2.6%)	5(3.2%)
- Death	0(0.0%)	1(1.3%)	1(0.6%)
- No Information on D14 given	0(0.0%)	2(2.6%)	2(1.3%)
- treated (D4-D13) with antimalarials although no fever and/or no parasites	0(0.0%)	0(0.0%)	0(0.0%)
Pat. in PP set	64(83.1%)	73(93.6%)	137(88.4%)
- Pat. who got the wrong concentration of MB	0(0.0%)	0(0.0%)	0(0.0%)
Pat. in PP set with correct concentraion of MB	64(83.1%)	73(93.6%)	137(88.4%)

% are based on all included patients

Table 12-4: Analysis sets and protocol compliance for Level 3

	2x daily N(%)	4x daily N(%)	Total N(%)
Included pat. (informed consent)	61(100.0%)	62(100.0%)	123(100.0%)
- Pat. without trial medication (Repeated vomiting)	8(13.1%)	0(0.0%)	8(6.5%)
- Pat. without trial medication (Other reason)	0(0.0%)	0(0.0%)	0(0.0%)
Pat. in FAS	53(86.9%)	62(100.0%)	115(93.5%)
- Pat. who vomited and the drug was not given again	2(3.3%)	2(3.2%)	4(3.3%)
- Pat. who vomited and it is unclear whether it was given again	0(0.0%)	0(0.0%)	0(0.0%)
- Pat. who violate inclusion/exclusion criteria	0(0.0%)	0(0.0%)	0(0.0%)
- Pat. without blue urine	0(0.0%)	0(0.0%)	0(0.0%)
- Withdrawal of informed consent	0(0.0%)	0(0.0%)	0(0.0%)
- Adverse event	0(0.0%)	0(0.0%)	0(0.0%)
- Investigators judgement	0(0.0%)	0(0.0%)	0(0.0%)
- Lost to follow up	1(1.6%)	1(1.6%)	2(1.6%)
- Death	0(0.0%)	0(0.0%)	0(0.0%)
- No Information on D14 given	3(4.9%)	7(11.3%)	10(8.1%)
- treated (D4-D13) with antimalarials although no fever and/or no parasites	0(0.0%)	0(0.0%)	0(0.0%)
Pat. in PP set	47(77.0%)	52(83.9%)	99(80.5%)
- Pat. who got the wrong concentration of MB	0(0.0%)	0(0.0%)	0(0.0%)
Pat. in PP set with correct concentraion of MB	47(77.0%)	52(83.9%)	99(80.5%)

% are based on all included patients

Table 12-5: Analysis sets and protocol compliance for all levels

	2x daily N(%)	4x daily N(%)	Total N(%)
Included pat. (informed consent)	217(100.0%)	218(100.0%)	435(100.0%)
- Pat. without trial medication (Repeated vomiting)	17(7.8%)	3(1.4%)	20(4.6%)
- Pat. without trial medication (Other reason)	3(1.4%)	0(0.0%)	3(0.7%)
Pat. in FAS	197(90.8%)	215(98.6%)	412(94.7%)
- Pat. who vomited and the drug was not given again	8(3.7%)	6(2.8%)	14(3.2%)
- Pat. who vomited and it is unclear whether it was given again	0(0.0%)	0(0.0%)	0(0.0%)
- Pat. who violate inclusion/exclusion criteria	0(0.0%)	1(0.5%)	1(0.2%)
- Pat. without blue urine	0(0.0%)	0(0.0%)	0(0.0%)
- Withdrawal of informed consent	1(0.5%)	0(0.0%)	1(0.2%)
- Adverse event	1(0.5%)	0(0.0%)	1(0.2%)
- Investigators judgement	1(0.5%)	0(0.0%)	1(0.2%)
- Lost to follow up	4(1.8%)	3(1.4%)	7(1.6%)
- Death	0(0.0%)	1(0.5%)	1(0.2%)
- No Information on D14 given	7(3.2%)	10(4.6%)	17(3.9%)
- treated (D4-D13) with antimalarials although no fever and/or no parasites	2(0.9%)	3(1.4%)	5(1.1%)
Pat. in PP set	173(79.7%)	191(87.6%)	364(83.7%)
- Pat. who got the wrong concentration of MB	17(7.8%)	19(8.7%)	36(8.3%)
Pat. in PP set with correct concentraion of MB	156(71.9%)	172(78.9%)	328(75.4%)

% are based on all included patients

Table 12-6: Demographics by group for Level 1 (FAS)

Characteristic	2x daily (N=72)	4x daily (N=75)	Total (N=147)
Sex			
- male	37(51.4%)	42(56.0%)	79(53.7%)
- female	35(48.6%)	33(44.0%)	68(46.3%)
Age[months]			
- N	72	75	147
- Mean +/- SD	33.7+/-16.0	29.5+/-15.9	31.6+/-16.0
- Median	36.0	31.0	34.0
- Min, Max	6.0, 59.0	6.0, 55.0	6.0, 59.0
Weight[kg]			
- N	72	75	147
- Mean +/- SD	12.2+/- 3.1	11.4+/- 3.1	11.8+/- 3.1
- Median	12.0	11.0	11.5
- Min, Max	7.0, 20.0	6.0, 17.5	6.0, 20.0
Other prior illnesses			
- No	59(84.3%)	65(86.7%)	124(85.5%)
- Yes	11(15.7%)	10(13.3%)	21(14.5%)
- Missing	2	0	2
Length of current disease episode[days]			
- N	71	74	145
- Mean +/- SD	2.0+/- 0.8	1.9+/- 0.8	1.9+/- 0.8
- Median	2.0	2.0	2.0
- Min, Max	1.0, 4.0	1.0, 4.0	1.0, 4.0
Prior treatment of current disease episode			
- No	48(66.7%)	44(58.7%)	92(62.6%)
- Yes	24(33.3%)	31(41.3%)	55(37.4%)
G6PD status (PCR method)			
- sufficient	56(77.8%)	56(75.7%)	112(76.7%)
- heterozygot deficient	9(12.5%)	9(12.2%)	18(12.3%)
- deficient	7(9.7%)	9(12.2%)	16(11.0%)
- Missing	0	1	1

Table 12-7: Demographics by group for Level 2 (FAS)

Characteristic	2x daily (N=72)	4x daily (N=78)	Total (N=150)
Sex			
- male	36(50.0%)	39(50.0%)	75(50.0%)
- female	36(50.0%)	39(50.0%)	75(50.0%)
Age[months]			
- N	72	78	150
- Mean +/- SD	32.5+/-14.6	31.8+/-14.6	32.1+/-14.5
- Median	33.5	34.0	34.0
- Min, Max	6.0, 58.0	6.0, 59.0	6.0, 59.0
Weight[kg]			
- N	72	78	150
- Mean +/- SD	11.8+/- 3.0	12.0+/- 3.1	11.9+/- 3.1
- Median	12.0	12.0	12.0
- Min, Max	7.0, 18.0	6.0, 20.0	6.0, 20.0
Other prior illnesses			
- No	53(73.6%)	53(67.9%)	106(70.7%)
- Yes	19(26.4%)	25(32.1%)	44(29.3%)
Length of current disease episode[days]			
- N	72	78	150
- Mean +/- SD	2.4+/- 1.0	2.6+/- 1.7	2.5+/- 1.4
- Median	2.0	2.0	2.0
- Min, Max	1.0, 7.0	1.0, 14.0	1.0, 14.0
Prior treatment of current disease episode			
- No	53(73.6%)	52(66.7%)	105(70.0%)
- Yes	19(26.4%)	26(33.3%)	45(30.0%)
G6PD status (PCR method)			
- sufficient	56(77.8%)	61(78.2%)	117(78.0%)
- heterozygot deficient	13(18.1%)	11(14.1%)	24(16.0%)
- deficient	3(4.2%)	6(7.7%)	9(6.0%)

Table 12-8: Demographics by group for Level 3 (FAS)

Characteristic	2x daily (N=53)	4x daily (N=62)	Total (N=115)
Sex			
- male	24(45.3%)	40(64.5%)	64(55.7%)
- female	29(54.7%)	22(35.5%)	51(44.3%)
Age[months]			
- N	53	62	115
- Mean +/- SD	39.2+/-12.5	35.0+/-14.9	36.9+/-13.9
- Median	38.0	36.0	36.0
- Min, Max	7.0, 58.0	8.0, 59.0	7.0, 59.0
Weight[kg]			
- N	53	62	115
- Mean +/- SD	13.2+/- 3.0	12.0+/- 2.6	12.5+/- 2.8
- Median	13.0	12.0	12.0
- Min, Max	7.0, 19.0	6.5, 17.0	6.5, 19.0
Other prior illnesses			
- No	46(86.8%)	45(72.6%)	91(79.1%)
- Yes	7(13.2%)	17(27.4%)	24(20.9%)
Length of current disease episode[days]			
- N	53	62	115
- Mean +/- SD	2.2+/- 1.0	2.4+/- 1.0	2.3+/- 1.0
- Median	2.0	2.0	2.0
- Min, Max	1.0, 5.0	1.0, 5.0	1.0, 5.0
Prior treatment of current disease episode			
- No	42(79.2%)	48(77.4%)	90(78.3%)
- Yes	11(20.8%)	14(22.6%)	25(21.7%)
G6PD status (PCR method)			
- sufficient	42(80.8%)	50(82.0%)	92(81.4%)
- heterozygot deficient	5(9.6%)	3(4.9%)	8(7.1%)
- deficient	5(9.6%)	8(13.1%)	13(11.5%)
- Missing	1	1	2

Table 12-9: Demographics by group for all Levels (FAS)

Characteristic	2x daily (N=197)	4x daily (N=215)	Total (N=412)
Sex			p_{Chi}=0.1527
- male	97(49.2%)	121(56.3%)	218(52.9%)
- female	100(50.8%)	94(43.7%)	194(47.1%)
Age[months]			p_{WMW}=0.0613
- N	197	215	412
- Mean +/- SD	34.7+/-14.8	31.9+/-15.2	33.3+/-15.1
- Median	36.0	35.0	35.5
- Min, Max	6.0, 59.0	6.0, 59.0	6.0, 59.0
Weight[kg]			p_{WMW}=0.1226
- N	197	215	412
- Mean +/- SD	12.3+/- 3.0	11.8+/- 3.0	12.1+/- 3.0
- Median	12.0	12.0	12.0
- Min, Max	7.0, 20.0	6.0, 20.0	6.0, 20.0
Other prior illnesses			p_{Chi}=0.2011
- No	158(81.0%)	163(75.8%)	321(78.3%)
- Yes	37(19.0%)	52(24.2%)	89(21.7%)
- Missing	2	0	2
Length of current disease episode[days]			p_{WMW}=0.8046
- N	196	214	410
- Mean +/- SD	2.2+/- 0.9	2.3+/- 1.3	2.2+/- 1.1
- Median	2.0	2.0	2.0
- Min, Max	1.0, 7.0	1.0, 14.0	1.0, 14.0
Prior treatment of current disease episode			p_{Chi}=0.2158
- No	143(72.6%)	144(67.0%)	287(69.7%)
- Yes	54(27.4%)	71(33.0%)	125(30.3%)
G6PD status (PCR method)			p_{Chi}=0.4011
- sufficient	154(78.6%)	167(78.4%)	321(78.5%)
- heterozygot deficient	27(13.8%)	23(10.8%)	50(12.2%)
- deficient	15(7.7%)	23(10.8%)	38(9.3%)
- Missing	1	2	3

Table 12-10: Baseline laboratory by group for Level 1 (FAS)

Characteristic	2x daily (N=72)	4x daily (N=75)	Total (N=147)
Haemoglobin[g/dl]			
- N	72	75	147
- Mean +/- SD	9.7+/- 1.1	9.7+/- 1.1	9.7+/- 1.1
- Median	9.5	9.8	9.6
- Min, Max	8.1, 14.2	6.9, 14.1	6.9, 14.2
MetHb[%]			
- N	72	75	147
- Mean +/- SD	1.4+/- 0.6	1.5+/- 0.6	1.5+/- 0.6
- Median	1.4	1.5	1.4
- Min, Max	0.2, 2.9	0.4, 2.9	0.2, 2.9
P. falciparum[/µl]			
- N	72	75	147
- Mean +/- SD	34616.7+/-24055.0	32662.4+/-27448.9	33619.6+/-25772.8
- Median	25000.0	26000.0	25000.0
- Min, Max	2600.0, 95000.0	1050.0, 98000.0	1050.0, 98000.0

Table 12-11: Baseline laboratory by group for Level 2 (FAS)

Characteristic	2x daily (N=72)	4x daily (N=78)	Total (N=150)
Haemoglobin[g/dl]			
- N	72	78	150
- Mean +/- SD	9.5+/- 1.0	9.7+/- 1.2	9.6+/- 1.1
- Median	9.4	9.5	9.4
- Min, Max	8.0, 12.5	8.0, 14.1	8.0, 14.1
MetHb[%]			
- N	72	78	150
- Mean +/- SD	1.1+/- 0.4	1.0+/- 0.4	1.1+/- 0.4
- Median	1.0	1.0	1.0
- Min, Max	0.4, 2.6	0.3, 2.3	0.3, 2.6
P. falciparum[/µl]			
- N	72	78	150
- Mean +/- SD	31913.9+/-27945.4	31159.0+/-23504.1	31521.3+/-25646.9
- Median	22750.0	26250.0	25000.0
- Min, Max	2000.0, 96500.0	2000.0, 96000.0	2000.0, 96500.0

Table 12-12: Baseline laboratory by group for Level 3 (FAS)

Characteristic	2x daily (N=53)	4x daily (N=62)	Total (N=115)
Haemoglobin[g/dl]			
- N	53	62	115
- Mean +/- SD	9.6+/- 0.9	9.4+/- 0.8	9.5+/- 0.8
- Median	9.5	9.3	9.4
- Min, Max	8.0, 11.5	8.0, 11.1	8.0, 11.5
MetHb[%]			
- N	53	62	115
- Mean +/- SD	1.1+/- 0.4	1.1+/- 0.5	1.1+/- 0.5
- Median	1.1	1.0	1.0
- Min, Max	0.3, 2.1	0.2, 2.6	0.2, 2.6
P. falciparum[/µl]			
- N	53	62	115
- Mean +/- SD	38981.1+/-27084.3	29477.4+/-25169.4	33857.4+/-26386.0
- Median	32000.0	19000.0	23000.0
- Min, Max	2500.0, 100000	2000.0, 90000.0	2000.0, 100000

Table 12-13: Baseline laboratory by group for all Levels (FAS)

Characteristic	2x daily (N=197)	4x daily (N=215)	Total (N=412)
Haemoglobin[g/dl]			p_{WMW}=0.8443
- N	197	215	412
- Mean +/- SD	9.6+/- 1.0	9.6+/- 1.1	9.6+/- 1.0
- Median	9.5	9.5	9.5
- Min, Max	8.0, 14.2	6.9, 14.1	6.9, 14.2
MetHb[%]			p_{WMW}=0.8166
- N	197	215	412
- Mean +/- SD	1.2+/- 0.5	1.2+/- 0.5	1.2+/- 0.5
- Median	1.1	1.1	1.1
- Min, Max	0.2, 2.9	0.2, 2.9	0.2, 2.9
P. falciparum[/µl]			p_{WMW}=0.2217
- N	197	215	412
- Mean +/- SD	34803.0+/-26361.4	31198.5+/-25327.9	32922.0+/-25858.6
- Median	25500.0	24000.0	24800.0
- Min, Max	2000.0, 100000	1050.0, 98000.0	1050.0, 100000

Table 12-14: Compliance by group for Level 1 (FAS)

	2x daily (N=72)	4x daily (N=75)
Number of Pat. with drug intake (1)		
- Day1	69(95.8%)	70(93.3%)
- Day1, Day2	68(94.4%)	70(93.3%)
- Day1, Day2, Day3	68(94.4%)	70(93.3%)
Blue urine at least once		
- Yes	70(97.2%)	74(98.7%)
- No	0(0.0%)	0(0.0%)
- not applicable	2(2.8%)	1(1.3%)
Time to treatment[hour]		
- N	72	75
- Mean +/- SD	2.3+/-0.8	2.3+/-0.7
- Median	2.3	2.1
- p5, p25, p75, p95	1.2, 1.8, 2.7, 3.8	1.4, 1.8, 2.6, 3.7
- Min, Max	0.5, 5.2	1.3, 4.2

time to treatment: from first lab measurement to first treatment

Table 12-15: Compliance by group for Level 2 (FAS)

	2x daily (N=72)	4x daily (N=78)
Number of Pat. with drug intake (1)		
- Day1	68(94.4%)	77(98.7%)
- Day1, Day2	67(93.1%)	77(98.7%)
- Day1, Day2, Day3	67(93.1%)	77(98.7%)
Blue urine at least once		
- Yes	70(97.2%)	77(98.7%)
- No	0(0.0%)	0(0.0%)
- not applicable	2(2.8%)	1(1.3%)
Time to treatment[hour]		
- N	72	78
- Mean +/- SD	1.9+/-0.5	2.0+/-0.5
- Median	1.9	2.1
- p5, p25, p75, p95	1.2, 1.6, 2.3, 2.9	1.2, 1.5, 2.3, 3.0
- Min, Max	1.2, 3.2	1.1, 3.4

time to treatment: from first lab measurement to first treatment

Table 12-16: Compliance by group for Level 3 (FAS)

	2x daily (N=53)	4x daily (N=62)
Number of Pat. with drug intake (1)		
- Day1	52(98.1%)	61(98.4%)
- Day1, Day2	51(96.2%)	60(96.8%)
- Day1, Day2, Day3	51(96.2%)	60(96.8%)
Blue urine at least once		
- Yes	51(96.2%)	61(98.4%)
- No	0(0.0%)	0(0.0%)
- not applicable	2(3.8%)	1(1.6%)
Time to treatment[hour]		
- N	53	62
- Mean +/- SD	1.6+/-0.5	1.5+/-0.4
- Median	1.6	1.5
- p5, p25, p75, p95	0.9, 1.3, 2.0, 2.6	1.0, 1.2, 1.8, 2.3
- Min, Max	0.6, 2.8	0.7, 2.9

time to treatment: from first lab measurement to first treatment

Table 12-17: Compliance by group for all Levels (FAS)

	2x daily (N=197)	4x daily (N=215)
Number of Pat. with drug intake (1)		
- Day1	189(95.9%)	208(96.7%)
- Day1, Day2	186(94.4%)	207(96.3%)
- Day1, Day2, Day3	186(94.4%)	207(96.3%)
Blue urine at least once		
- Yes	191(97.0%)	212(98.6%)
- No	0(0.0%)	0(0.0%)
- not applicable	6(3.0%)	3(1.4%)
Time to treatment[hour]		
- N	197	215
- Mean +/- SD	2.0+/-0.7	2.0+/-0.6
- Median	1.9	1.9
- p5, p25, p75, p95	1.1, 1.5, 2.3, 3.1	1.1, 1.5, 2.3, 3.1
- Min, Max	0.5, 5.2	0.7, 4.2

time to treatment: from first lab measurement to first treatment

Table 12-18: Changes from baseline in lab-data by study day for level 1 (2x daily, FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline
Haemoglobin[g/dl]				
- N	72	68	68	67
- Mean +/- SD	-0.6+/-0.7	-0.8+/-0.6	-0.8+/-0.7	-0.2+/-1.0
- Median	-0.5	-0.7	-0.8	-0.2
- p5, p25, p75, p95	-1.5, -0.9, -0.2, 0.1	-1.5, -1.0, -0.4, 0.0	-1.7, -1.3, -0.5, 0.3	-1.6, -0.9, 0.3, 1.6
- Min, Max	-4.1, 0.5	-3.5, 0.6	-3.5, 0.8	-2.6, 1.9
- 95% CI mean	(-0.7; -0.4)	(-0.9; -0.6)	(-1.0; -0.7)	(-0.4; 0.0)
- 95% CI median	(-0.6; -0.3)	(-0.9; -0.6)	(-1.0; -0.6)	(-0.4; 0.1)
- p-Value (1)	<.0001	<.0001	<.0001	0.1058
P. falciparum[/µl]				
- N	72	68	68	67
- Mean +/- SD	-7953.5+/-45415.3	-32687.4+/-24812.5	-34878.1+/-23683.5	-30985.1+/-29618.0
- Median	-11150.0	-25890.0	-26000.0	-25000.0
- p5, p25, p75, p95	-49900.0, -27750.0, -2150.0, 42500.0	-77450.0, -48000.0, -16750.0, 6000.0	-78500.0, -51530.0, -18750.0, -4500.0	-78500.0, -52600.0, -15000.0, 23000.0
- Min, Max	-76000.0, 231600.0	-95000.0, 13000.0	-95000.0, -2600.0	-95000.0, 41000.0
- 95% CI mean	(-18625.6; 2718.6)	(-38693.2; -26681.5)	(-40610.8; -29145.5)	(-38209.5; -23760.7)
- 95% CI median	(-18700.0; -7500.0)	(-42000.0; -21000.0)	(-43700.0; -21000.0)	(-42400.0; -21000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]				
- N	72	68	68	67
- Mean +/- SD	-0.7+/-1.3	-5.3+/-3.6	-8.4+/-3.1	-7.7+/-4.1
- Median	-0.7	-4.5	-9.9	-9.9
- p5, p25, p75, p95	-2.7, -1.3, -0.2, 1.5	-11.2, -9.4, -2.8, 0.6	-11.3, -10.7, -5.4, -2.5	-11.2, -10.7, -4.3, 1.0
- Min, Max	-5.3, 2.9	-11.5, 1.2	-11.5, -1.2	-11.5, 1.8
- 95% CI mean	(-1.0; -0.4)	(-6.1; -4.4)	(-9.1; -7.6)	(-8.7; -6.7)
- 95% CI median	(-1.0; -0.4)	(-5.4; -3.5)	(-10.1; -9.0)	(-10.1; -8.9)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15

Table 12-19: Changes from baseline in lab-data by study day for level 2 (2x daily, FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline
Haemoglobin[g/dl]				
- N	71	68	67	64
- Mean +/- SD	-0.5+/-0.7	-0.6+/-0.8	-0.7+/-0.9	-0.1+/-1.0
- Median	-0.5	-0.7	-0.5	-0.1
- p5, p25, p75, p95	-1.7, -0.9, 0.0, 0.5	-2.1, -1.2, -0.1, 0.4	-2.6, -1.3, -0.2, 0.5	-1.6, -0.8, 0.6, 1.5
- Min, Max	-2.2, 1.2	-2.3, 1.3	-2.7, 1.2	-1.9, 2.2
- 95% CI mean	(-0.6; -0.3)	(-0.8; -0.5)	(-0.9; -0.4)	(-0.3; 0.1)
- 95% CI median	(-0.7; -0.4)	(-0.8; -0.4)	(-0.7; -0.3)	(-0.4; 0.0)
- p-Value (1)	<.0001	<.0001	<.0001	0.3081
P. falciparum[/µl]				
- N	71	68	67	64
- Mean +/- SD	-14252.1+/-26194.9	-28979.6+/-26242.1	-30295.8+/-27212.2	-25037.2+/-28635.5
- Median	-9000.0	-18600.0	-21000.0	-16500.0
- p5, p25, p75, p95	-58000.0, -28000.0, 1500.0, 16500.0	-89010.0, -44275.0, -8675.0, -2200.0	-89500.0, -47000.0, -9000.0, -2400.0	-85000.0, -42000.0, -6300.0, 10500.0
- Min, Max	-80000.0, 92000.0	-95890.0, -1500.0	-96500.0, 9000.0	-90000.0, 42000.0
- 95% CI mean	(-20452.4; -8051.9)	(-35331.5; -22627.6)	(-36933.4; -23658.2)	(-32190.1; -17884.3)
- 95% CI median	(-15000.0; -4500.0)	(-30000.0; -12500.0)	(-30800.0; -13000.0)	(-29000.0; -11500.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]				
- N	71	68	67	64
- Mean +/- SD	-0.7+/-1.2	-4.9+/-2.6	-8.4+/-2.8	-6.6+/-4.3
- Median	-0.7	-4.6	-9.4	-8.7
- p5, p25, p75, p95	-2.8, -1.4, 0.1, 1.1	-9.5, -6.0, -3.0, -1.3	-11.3, -10.4, -7.6, -3.2	-11.4, -10.2, -1.9, 0.3
- Min, Max	-4.1, 2.0	-11.4, -0.4	-11.5, 0.5	-11.4, 3.1
- 95% CI mean	(-1.0; -0.4)	(-5.5; -4.3)	(-9.0; -7.7)	(-7.7; -5.5)
- 95% CI median	(-0.9; -0.5)	(-5.2; -4.1)	(-9.7; -8.6)	(-9.5; -5.4)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15

Table 12-20: Changes from baseline in lab-data by study day for level 3 (2x daily, FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline	Day28-Baseline
Haemoglobin[g/dl]					
- N	53	52	51		
- Mean +/- SD	-0.5+/-0.6	-0.8+/-0.8	-0.7+/-0.8		
- Median	-0.6	-0.8	-0.7		
- p5, p25, p75, p95	-1.6, -0.9, -0.1, 0.5	-2.0, -1.3, -0.3, 0.7	-2.2, -1.2, -0.2, 0.4		
- Min, Max	-2.2, 0.6	-2.2, 1.3	-2.8, 1.2		
- 95% CI mean	(-0.7; -0.4)	(-1.0; -0.6)	(-0.9; -0.5)		
- 95% CI median	(-0.8; -0.4)	(-1.1; -0.5)	(-0.9; -0.4)		
- p-Value (1)	<.0001	<.0001	<.0001		
P. falciparum[/µl]					
- N	53	52	51	50	49
- Mean +/- SD	-22994.3+/-23786.6	-39027.3+/-26841.7	-39185.3+/-27273.0	-38807.0+/-27134.8	-32704.1+/-33603.1
- Median	-18500.0	-32650.0	-32000.0	-31350.0	-23000.0
- p5, p25, p75, p95	-75000.0, -35500.0, -6500.0, 3000.0	-89750.0, -57750.0, -17650.0, -4350.0	-90000.0, -58000.0, -17000.0, -4500.0	-89800.0, -61000.0, -17000.0, -4500.0	-90000.0, -54500.0, -15500.0, 18000.0
- Min, Max	-83000.0, 12500.0	-99700.0, -2500.0	-100000, -2500.0	-100000, -2500.0	-100000, 82000.0
- 95% CI mean	(-29550.7; -16437.9)	(-46500.1; -31554.5)	(-46855.9; -31514.6)	(-46518.6; -31095.4)	(-42356.0; -23052.1)
- 95% CI median	(-24500.0; -8000.0)	(-46800.0; -20900.0)	(-43500.0; -21000.0)	(-43500.0; -20000.0)	(-40000.0; -19500.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]					
- N	53	52	51	50	49
- Mean +/- SD	-1.2+/-1.5	-5.5+/-2.2	-9.5+/-2.1	-8.5+/-2.9	-7.4+/-4.3
- Median	-0.9	-4.8	-10.0	-9.9	-9.9
- p5, p25, p75, p95	-3.6, -1.7, -0.3, 0.3	-10.4, -5.8, -4.0, -3.2	-11.4, -10.8, -9.4, -5.0	-11.4, -10.6, -5.9, -2.5	-11.4, -10.6, -3.3, 0.3
- Min, Max	-9.3, 0.6	-11.2, -2.0	-11.5, -1.8	-11.5, -1.8	-11.5, 2.5
- 95% CI mean	(-1.6; -0.8)	(-6.1; -4.9)	(-10.1; -8.9)	(-9.3; -7.7)	(-8.6; -6.1)
- 95% CI median	(-1.2; -0.6)	(-5.5; -4.5)	(-10.6; -9.9)	(-10.0; -9.1)	(-10.3; -7.8)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15 / Day28 is including Day 25-30

Table 12-21: Changes from baseline in lab-data by WHO-Day for level 1 (2x daily, FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
Haemoglobin[g/dl]				
- N	68	68		63
- Mean +/- SD	-0.8+/-0.6	-0.8+/-0.7		-0.2+/-1.0
- Median	-0.7	-0.8		-0.2
- p5, p25, p75, p95	-1.5, -1.0, -0.4, 0.0	-1.7, -1.3, -0.5, 0.3		-1.6, -0.9, 0.3, 1.6
- Min, Max	-3.5, 0.6	-3.5, 0.8		-2.6, 1.9
- 95% CI mean	(-0.9; -0.6)	(-1.0; -0.7)		(-0.4; 0.1)
- 95% CI median	(-0.9; -0.6)	(-1.0; -0.6)		(-0.4; 0.2)
- p-Value (1)	<.0001	<.0001		0.1657
P. falciparum[/µl]				
- N	68	68	68	63
- Mean +/- SD	-32687.4+/-24812.5	-34878.1+/-23683.5	-35471.3+/-23977.1	-32127.0+/-29579.6
- Median	-25890.0	-26000.0	-26000.0	-27000.0
- p5, p25, p75, p95	-77450.0, -48000.0, -16750.0, 6000.0	-78500.0, -51530.0, -18750.0, -4500.0	-78500.0, -52050.0, -19000.0, -4500.0	-78500.0, -55900.0, -16000.0, 16700.0
- Min, Max	-95000.0, 13000.0	-95000.0, -2600.0	-95000.0, -2600.0	-95000.0, 41000.0
- 95% CI mean	(-38693.2; -26681.5)	(-40610.8; -29145.5)	(-41275.0; -29667.6)	(-39576.5; -24677.5)
- 95% CI median	(-42000.0; -21000.0)	(-43700.0; -21000.0)	(-44000.0; -21500.0)	(-42400.0; -21000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-22: Changes from baseline in lab-data by WHO-Day for level 2 (2x daily, FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
Haemoglobin[g/dl]				
- N	68	67		64
- Mean +/- SD	-0.6+/-0.8	-0.7+/-0.9		-0.1+/-1.0
- Median	-0.7	-0.5		-0.1
- p5, p25, p75, p95	-2.1, -1.2, -0.1, 0.4	-2.6, -1.3, -0.2, 0.5		-1.6, -0.8, 0.6, 1.5
- Min, Max	-2.3, 1.3	-2.7, 1.2		-1.9, 2.2
- 95% CI mean	(-0.8; -0.5)	(-0.9; -0.4)		(-0.3; 0.1)
- 95% CI median	(-0.8; -0.4)	(-0.7; -0.3)		(-0.4; 0.0)
- p-Value (1)	<.0001	<.0001		0.3081
P. falciparum[/µl]				
- N	68	68	67	64
- Mean +/- SD	-28916.3+/-26303.9	-29935.6+/-27171.3	-30769.4+/-27120.6	-25037.2+/-28635.5
- Median	-18600.0	-20500.0	-22000.0	-16500.0
- p5, p25, p75, p95	-89010.0, -44275.0, -8675.0, -2000.0	-89500.0, -46000.0, -8600.0, -2400.0	-89850.0, -47000.0, -10000.0, -2500.0	-85000.0, -42000.0, -6300.0, 10500.0
- Min, Max	-95890.0, -1500.0	-96500.0, 9000.0	-96500.0, -2000.0	-90000.0, 42000.0
- 95% CI mean	(-35283.2; -22549.4)	(-36512.4; -23358.7)	(-37384.6; -24154.2)	(-32190.1; -17884.3)
- 95% CI median	(-30000.0; -12500.0)	(-30800.0; -13000.0)	(-31000.0; -13000.0)	(-29000.0; -11500.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-23: Changes from baseline in lab-data by WHO-Day for level 3 (2x daily, FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline	D28-Baseline
Haemoglobin[g/dl]					
- N	52	51			
- Mean +/- SD	-0.8+/-0.8	-0.7+/-0.8			
- Median	-0.8	-0.7			
- p5, p25, p75, p95	-2.0, -1.3, -0.3, 0.7	-2.2, -1.2, -0.2, 0.4			
- Min, Max	-2.2, 1.3	-2.8, 1.2			
- 95% CI mean	(-1.0; -0.6)	(-0.9; -0.5)			
- 95% CI median	(-1.1; -0.5)	(-0.9; -0.4)			
- p-Value (1)	<.0001	<.0001			
P. falciparum[/µl]					
- N	52	51	51	46	49
- Mean +/- SD	-39027.3+/-26841.7	-39185.3+/-27273.0	-39268.6+/-27261.1	-39357.6+/-27103.0	-32704.1+/-33603.1
- Median	-32650.0	-32000.0	-32000.0	-31350.0	-23000.0
- p5, p25, p75, p95	-89750.0, -57750.0, -17650.0, -4350.0	-90000.0, -58000.0, -17000.0, -4500.0	-90000.0, -59750.0, -17000.0, -4500.0	-89800.0, -61000.0, -17000.0, -9000.0	-90000.0, -54500.0, -15500.0, 18000.0
- Min, Max	-99700.0, -2500.0	-100000, -2500.0	-100000, -2500.0	-100000, -3500.0	-100000, 82000.0
- 95% CI mean	(-46500.1; -31554.5)	(-46855.9; -31514.6)	(-46935.9; -31601.3)	(-47406.2; -31309.0)	(-42356.0; -23052.1)
- 95% CI median	(-46800.0; -20900.0)	(-43500.0; -21000.0)	(-43500.0; -21000.0)	(-46850.0; -20000.0)	(-40000.0; -19500.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-24: Changes from baseline in lab-data by study day for level 1 (4x daily, FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline
Haemoglobin[g/dl]				
- N	73	70	70	70
- Mean +/- SD	-0.6+/-0.8	-0.9+/-0.9	-0.8+/-0.9	-0.2+/-1.3
- Median	-0.6	-0.8	-0.7	-0.2
- p5, p25, p75, p95	-1.5, -1.0, -0.1, 0.3	-2.4, -1.3, -0.4, 0.1	-2.4, -1.2, -0.2, 0.2	-2.5, -0.9, 0.5, 1.6
- Min, Max	-5.2, 1.4	-5.7, 0.8	-5.3, 0.8	-4.9, 3.0
- 95% CI mean	(-0.8; -0.4)	(-1.1; -0.7)	(-1.0; -0.6)	(-0.5; 0.1)
- 95% CI median	(-0.8; -0.3)	(-0.9; -0.6)	(-0.9; -0.6)	(-0.5; 0.2)
- p-Value (1)	<.0001	<.0001	<.0001	0.1651
P. falciparum[/µl]				
- N	73	70	70	70
- Mean +/- SD	-8110.0+/-31926.4	-32960.0+/-27673.9	-33634.9+/-27824.9	-32079.6+/-28308.6
- Median	-9200.0	-26425.0	-27250.0	-23500.0
- p5, p25, p75, p95	-59000.0, -22000.0, 500.0, 34000.0	-89750.0, -52500.0, -9500.0, -2100.0	-90500.0, -54100.0, -9540.0, -2500.0	-90000.0, -54500.0, -7200.0, -2000.0
- Min, Max	-78000.0, 137500.0	-97230.0, 5500.0	-97950.0, -2000.0	-98000.0, 13800.0
- 95% CI mean	(-15559.0; -661.0)	(-39558.6; -26361.4)	(-40269.5; -27000.2)	(-38829.5; -25329.6)
- 95% CI median	(-13000.0; -3900.0)	(-34000.0; -17800.0)	(-34000.0; -18000.0)	(-33000.0; -16500.0)
- p-Value (1)	0.0005	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]				
- N	73	70	70	70
- Mean +/- SD	-0.8+/-1.5	-5.1+/-2.6	-8.7+/-2.7	-8.2+/-3.4
- Median	-0.6	-4.6	-9.7	-9.6
- p5, p25, p75, p95	-3.1, -1.3, 0.1, 1.0	-10.3, -6.6, -3.3, -1.8	-11.4, -10.7, -7.6, -2.5	-11.3, -10.7, -7.6, -0.6
- Min, Max	-8.5, 2.6	-11.4, 0.9	-11.4, -1.9	-11.5, 0.5
- 95% CI mean	(-1.1; -0.4)	(-5.7; -4.5)	(-9.3; -8.0)	(-9.0; -7.4)
- 95% CI median	(-1.0; -0.3)	(-5.1; -4.2)	(-10.2; -8.9)	(-10.0; -8.8)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15

Table 12-25: Changes from baseline in lab-data by study day for level 2 (4x daily, FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline
Haemoglobin[g/dl]				
- N	77	77	77	73
- Mean +/- SD	-0.6+/-0.7	-0.9+/-0.8	-1.0+/-1.0	-0.5+/-1.2
- Median	-0.6	-0.9	-1.0	-0.3
- p5, p25, p75, p95	-1.7, -1.1, -0.1, 0.3	-2.2, -1.5, -0.3, 0.2	-2.8, -1.6, -0.2, 0.5	-2.5, -1.1, 0.3, 1.3
- Min, Max	-2.2, 1.0	-2.8, 0.4	-3.4, 1.7	-4.4, 2.2
- 95% CI mean	(-0.8; -0.5)	(-1.1; -0.8)	(-1.2; -0.7)	(-0.7; -0.2)
- 95% CI median	(-0.9; -0.4)	(-1.2; -0.6)	(-1.1; -0.7)	(-0.7; 0.0)
- p-Value (1)	<.0001	<.0001	<.0001	0.0029
P. falciparum[/µl]				
- N	77	77	77	74
- Mean +/- SD	-12550.6+/-26205.5	-30259.0+/-23479.0	-30571.3+/-24060.7	-29309.5+/-24410.5
- Median	-11500.0	-23500.0	-25000.0	-23250.0
- p5, p25, p75, p95	-53900.0, -25500.0, -500.0, 30500.0	-85950.0, -45700.0, -12750.0, -3500.0	-86000.0, -46500.0, -12800.0, -2500.0	-86000.0, -45000.0, -10300.0, -2500.0
- Min, Max	-92500.0, 82000.0	-96000.0, -1400.0	-96000.0, 14000.0	-96000.0, 14000.0
- 95% CI mean	(-18498.6; -6602.7)	(-35588.1; -24929.9)	(-36032.4; -25110.2)	(-34964.9; -23654.0)
- 95% CI median	(-14900.0; -3900.0)	(-31800.0; -17700.0)	(-32500.0; -18000.0)	(-30500.0; -16000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]				
- N	77	77	77	74
- Mean +/- SD	-0.9+/-1.2	-5.6+/-3.2	-8.6+/-2.9	-8.0+/-3.6
- Median	-0.8	-4.5	-9.6	-9.6
- p5, p25, p75, p95	-3.5, -1.5, -0.1, 1.2	-10.8, -8.5, -3.2, -1.2	-11.4, -10.5, -8.2, -2.2	-11.2, -10.4, -6.1, -0.3
- Min, Max	-5.0, 1.5	-11.5, -0.4	-11.5, 0.4	-11.5, 1.6
- 95% CI mean	(-1.1; -0.6)	(-6.3; -4.8)	(-9.2; -7.9)	(-8.8; -7.2)
- 95% CI median	(-0.9; -0.5)	(-5.4; -3.9)	(-10.0; -9.2)	(-10.0; -9.2)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15

Table 12-26: Changes from baseline in lab-data by study day for level 3 (4x daily, FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline	Day28-Baseline
Haemoglobin[g/dl]					
- N	62	61	61	1	
- Mean +/- SD	-0.5+/-0.6	-0.6+/-0.7	-0.6+/-0.9	-0.4+/-.	
- Median	-0.4	-0.5	-0.6	-0.4	
- p5, p25, p75, p95	-1.7, -0.6, -0.1, 0.4	-1.7, -1.0, -0.1, 0.3	-1.8, -1.1, 0.1, 0.6	-0.4, -0.4, -0.4, -0.4	
- Min, Max	-2.4, 1.0	-2.8, 1.0	-3.9, 1.1	-0.4, -0.4	
- 95% CI mean	(-0.6; -0.3)	(-0.8; -0.4)	(-0.8; -0.4)	(.; .)	
- 95% CI median	(-0.5; -0.3)	(-0.7; -0.3)	(-0.8; -0.1)	(.; .)	
- p-Value (1)	<.0001	<.0001	<.0001	1.0000	
P. falciparum[/µl]					
- N	62	61	61	59	59
- Mean +/- SD	-13184.5+/-25297.4	-29278.0+/-25239.8	-29597.5+/-25358.2	-26378.8+/-25490.7	-25135.6+/-24068.4
- Median	-8250.0	-19000.0	-19500.0	-17000.0	-16700.0
- p5, p25, p75, p95	-61000.0, -23000.0, -3000.0, 16500.0	-76610.0, -46000.0, -7900.0, -4000.0	-77000.0, -46000.0, -8000.0, -4000.0	-81000.0, -40500.0, -6000.0, 2000.0	-71000.0, -39300.0, -6000.0, 4500.0
- Min, Max	-83500.0, 90500.0	-89600.0, -2000.0	-90000.0, -2000.0	-90000.0, 19000.0	-78000.0, 25500.0
- 95% CI mean	(-19608.9; -6760.2)	(-35742.3; -22813.8)	(-36092.1; -23103.0)	(-33021.7; -19735.9)	(-31407.9; -18863.3)
- 95% CI median	(-13000.0; -4500.0)	(-29800.0; -13000.0)	(-30000.0; -13000.0)	(-26500.0; -12000.0)	(-26000.0; -12000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]					
- N	62	61	61	59	59
- Mean +/- SD	-1.1+/-1.1	-6.0+/-2.7	-9.1+/-2.0	-8.2+/-3.3	-7.0+/-4.0
- Median	-1.1	-5.0	-9.6	-9.5	-8.9
- p5, p25, p75, p95	-3.3, -1.7, -0.3, 0.5	-10.8, -8.5, -4.1, -2.9	-11.2, -10.5, -8.6, -5.2	-11.3, -10.4, -8.3, 0.3	-11.1, -10.3, -3.3, 0.6
- Min, Max	-4.0, 1.3	-11.2, -1.4	-11.4, -1.2	-11.4, 0.4	-11.3, 1.9
- 95% CI mean	(-1.4; -0.8)	(-6.7; -5.3)	(-9.7; -8.6)	(-9.1; -7.4)	(-8.0; -6.0)
- 95% CI median	(-1.4; -0.5)	(-6.3; -4.3)	(-9.9; -8.9)	(-9.7; -8.7)	(-9.6; -4.4)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15 / Day28 is including Day 25-30

Table 12-27: Changes from baseline in lab-data by WHO-Day for level 1 (4x daily, FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
Haemoglobin[g/dl]				
- N	70	70		69
- Mean +/- SD	-0.9+/-0.9	-0.8+/-0.9		-0.2+/-1.3
- Median	-0.8	-0.7		-0.2
- p5, p25, p75, p95	-2.4, -1.3, -0.4, 0.1	-2.4, -1.2, -0.2, 0.2		-2.5, -0.9, 0.5, 1.6
- Min, Max	-5.7, 0.8	-5.3, 0.8		-4.9, 3.0
- 95% CI mean	(-1.1; -0.7)	(-1.0; -0.6)		(-0.5; 0.1)
- 95% CI median	(-0.9; -0.6)	(-0.9; -0.6)		(-0.5; 0.2)
- p-Value (1)	<.0001	<.0001		0.1720
P. falciparum[/µl]				
- N	70	70	70	69
- Mean +/- SD	-32960.0+/-27673.9	-33634.9+/-27824.9	-33426.6+/-27895.7	-32240.1+/-28483.9
- Median	-26425.0	-27250.0	-26000.0	-26000.0
- p5, p25, p75, p95	-89750.0, -52500.0, -9500.0, -2100.0	-90500.0, -54100.0, -9540.0, -2500.0	-90500.0, -55400.0, -9700.0, -2500.0	-90000.0, -54500.0, -7200.0, -2000.0
- Min, Max	-97230.0, 5500.0	-97950.0, -2000.0	-98000.0, -2000.0	-98000.0, 13800.0
- 95% CI mean	(-39558.6; -26361.4)	(-40269.5; -27000.2)	(-40078.1; -26775.1)	(-39082.7; -25397.6)
- 95% CI median	(-34000.0; -17800.0)	(-34000.0; -18000.0)	(-34000.0; -18000.0)	(-33000.0; -16000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-28: Changes from baseline in lab-data by WHO-Day for level 2 (4x daily, FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
Haemoglobin[g/dl]				
- N	77	77	1	71
- Mean +/- SD	-0.9+/-0.8	-1.0+/-1.0	-2.8+/-.	-0.4+/-1.1
- Median	-0.9	-1.0	-2.8	-0.3
- p5, p25, p75, p95	-2.2, -1.5, -0.3, 0.2	-2.8, -1.6, -0.2, 0.5	-2.8, -2.8, -2.8, -2.8	-2.4, -1.2, 0.3, 1.3
- Min, Max	-2.8, 0.4	-3.4, 1.7	-2.8, -2.8	-3.5, 2.2
- 95% CI mean	(-1.1; -0.8)	(-1.2; -0.7)	(.; .)	(-0.7; -0.2)
- 95% CI median	(-1.2; -0.6)	(-1.1; -0.7)	(.; .)	(-0.7; 0.0)
- p-Value (1)	<.0001	<.0001	1.0000	0.0028
P. falciparum[/µl]				
- N	77	77	77	72
- Mean +/- SD	-30259.0+/-23479.0	-30571.3+/-24060.7	-31145.5+/-23575.6	-30340.3+/-24477.7
- Median	-23500.0	-25000.0	-25500.0	-25750.0
- p5, p25, p75, p95	-85950.0, -45700.0, -12750.0, -3500.0	-86000.0, -46500.0, -12800.0, -2500.0	-86000.0, -46500.0, -13000.0, -3400.0	-86000.0, -46550.0, -10500.0, -2500.0
- Min, Max	-96000.0, -1400.0	-96000.0, 14000.0	-96000.0, -1200.0	-96000.0, 14000.0
- 95% CI mean	(-35588.1; -24929.9)	(-36032.4; -25110.2)	(-36496.5; -25794.5)	(-36092.3; -24588.3)
- 95% CI median	(-31800.0; -17700.0)	(-32500.0; -18000.0)	(-32400.0; -18000.0)	(-32500.0; -17000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-29: Changes from baseline in lab-data by WHO-Day for level 3 (4x daily, FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline	D28-Baseline
Haemoglobin[g/dl]					
- N	61	61	1	2	
- Mean +/- SD	-0.6+/-0.7	-0.6+/-0.9	-4.0+/-.	-0.2+/-0.2	
- Median	-0.5	-0.6	-4.0	-0.2	
- p5, p25, p75, p95	-1.7, -1.0, -0.1, 0.3	-1.8, -1.1, 0.1, 0.6	-4.0, -4.0, -4.0, -4.0	-0.4, -0.4, -0.1, -0.1	
- Min, Max	-2.8, 1.0	-3.9, 1.1	-4.0, -4.0	-0.4, -0.1	
- 95% CI mean	(-0.8; -0.4)	(-0.8; -0.4)	(.; .)	(-2.2; 1.7)	
- 95% CI median	(-0.7; -0.3)	(-0.8; -0.1)	(.; .)	(-0.4; -0.1)	
- p-Value (1)	<.0001	<.0001	1.0000	0.5000	
P. falciparum[/µl]					
- N	61	61	60	53	59
- Mean +/- SD	-29278.0+/-25239.8	-29597.5+/-25358.2	-28949.2+/-25008.4	-25793.4+/-25052.9	-25135.6+/-24068.4
- Median	-19000.0	-19500.0	-18250.0	-17000.0	-16700.0
- p5, p25, p75, p95	-76610.0, -46000.0, -7900.0, -4000.0	-77000.0, -46000.0, -8000.0, -4000.0	-79000.0, -46000.0, -7750.0, -4000.0	-81000.0, -35000.0, -7500.0, 2000.0	-71000.0, -39300.0, -6000.0, 4500.0
- Min, Max	-89600.0, -2000.0	-90000.0, -2000.0	-90000.0, -2000.0	-90000.0, 19000.0	-78000.0, 25500.0
- 95% CI mean	(-35742.3; -22813.8)	(-36092.1; -23103.0)	(-35409.5; -22488.8)	(-32698.8; -18888.0)	(-31407.9; -18863.3)
- 95% CI median	(-29800.0; -13000.0)	(-30000.0; -13000.0)	(-34000.0; -14800.0)	(-26500.0; -13000.0)	(-26000.0; -12000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-30: Changes from baseline in lab-data by study day for level 1 (FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline
Haemoglobin[g/dl]				
- N	145	138	138	137
- Mean +/- SD	-0.6+/-0.7	-0.8+/-0.8	-0.8+/-0.8	-0.2+/-1.1
- Median	-0.5	-0.7	-0.7	-0.2
- p5, p25, p75, p95	-1.5, -0.9, -0.1, 0.1	-2.2, -1.2, -0.4, 0.1	-2.4, -1.2, -0.4, 0.3	-2.0, -0.9, 0.4, 1.6
- Min, Max	-5.2, 1.4	-5.7, 0.8	-5.3, 0.8	-4.9, 3.0
- 95% CI mean	(-0.7; -0.5)	(-1.0; -0.7)	(-1.0; -0.7)	(-0.4; -0.0)
- 95% CI median	(-0.6; -0.3)	(-0.8; -0.7)	(-0.8; -0.6)	(-0.4; 0.0)
- p-Value (1)	<.0001	<.0001	<.0001	0.0322
P. falciparum[/µl]				
- N	145	138	138	137
- Mean +/- SD	-8032.3+/-39071.8	-32825.7+/-26207.3	-34247.5+/-25780.6	-31544.3+/-28854.7
- Median	-9800.0	-26325.0	-26500.0	-25000.0
- p5, p25, p75, p95	-58500.0, -25500.0, -1000.0, 34000.0	-88900.0, -49000.0, -12400.0, -1500.0	-89500.0, -52600.0, -15000.0, -2800.0	-83000.0, -54000.0, -9500.0, 12500.0
- Min, Max	-78000.0, 231600.0	-97230.0, 13000.0	-97950.0, -2000.0	-98000.0, 41000.0
- 95% CI mean	(-14445.7; -1618.8)	(-37237.1; -28414.2)	(-38587.1; -29907.8)	(-36419.4; -26669.2)
- 95% CI median	(-12750.0; -7400.0)	(-31000.0; -20800.0)	(-33500.0; -21000.0)	(-31500.0; -20000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]				
- N	145	138	138	137
- Mean +/- SD	-0.8+/-1.4	-5.2+/-3.1	-8.5+/-2.9	-7.9+/-3.8
- Median	-0.7	-4.5	-9.8	-9.8
- p5, p25, p75, p95	-2.7, -1.3, -0.2, 1.0	-10.7, -7.6, -3.1, -0.3	-11.3, -10.7, -7.6, -2.5	-11.3, -10.7, -5.6, 0.5
- Min, Max	-8.5, 2.9	-11.5, 1.2	-11.5, -1.2	-11.5, 1.8
- 95% CI mean	(-1.0; -0.5)	(-5.7; -4.7)	(-9.0; -8.0)	(-8.6; -7.3)
- 95% CI median	(-0.9; -0.5)	(-4.8; -4.2)	(-10.0; -9.2)	(-10.0; -9.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15

Table 12-31: Changes from baseline in lab-data by study day for level 2 (FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline
Haemoglobin[g/dl]				
- N	148	145	144	137
- Mean +/- SD	-0.6+/-0.7	-0.8+/-0.8	-0.8+/-0.9	-0.3+/-1.1
- Median	-0.6	-0.8	-0.7	-0.2
- p5, p25, p75, p95	-1.7, -1.0, -0.1, 0.5	-2.2, -1.4, -0.2, 0.3	-2.6, -1.5, -0.2, 0.5	-2.2, -1.0, 0.4, 1.4
- Min, Max	-2.2, 1.2	-2.8, 1.3	-3.4, 1.7	-4.4, 2.2
- 95% CI mean	(-0.7; -0.5)	(-0.9; -0.7)	(-1.0; -0.7)	(-0.5; -0.1)
- 95% CI median	(-0.8; -0.5)	(-0.9; -0.6)	(-0.9; -0.5)	(-0.4; -0.1)
- p-Value (1)	<.0001	<.0001	<.0001	0.0041
P. falciparum[/µl]				
- N	148	145	144	138
- Mean +/- SD	-13366.9+/-26125.1	-29659.0+/-24734.0	-30443.1+/-25484.6	-27328.1+/-26441.6
- Median	-10500.0	-21820.0	-23850.0	-20500.0
- p5, p25, p75, p95	-53900.0, -27250.0, -400.0, 23000.0	-85950.0, -44800.0, -10320.0, -2400.0	-86000.0, -46700.0, -11000.0, -2500.0	-86000.0, -43800.0, -9300.0, -1250.0
- Min, Max	-92500.0, 92000.0	-96000.0, -1400.0	-96500.0, 14000.0	-96000.0, 42000.0
- 95% CI mean	(-17610.8; -9123.0)	(-33719.0; -25599.0)	(-34641.1; -26245.2)	(-31779.0; -22877.2)
- 95% CI median	(-13500.0; -6000.0)	(-28950.0; -16000.0)	(-30000.0; -17000.0)	(-27000.0; -15000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]				
- N	148	145	144	138
- Mean +/- SD	-0.8+/-1.2	-5.3+/-2.9	-8.5+/-2.8	-7.4+/-4.0
- Median	-0.7	-4.6	-9.5	-9.3
- p5, p25, p75, p95	-3.2, -1.4, -0.0, 1.1	-10.8, -7.1, -3.2, -1.3	-11.3, -10.5, -7.7, -2.9	-11.3, -10.3, -3.9, -0.2
- Min, Max	-5.0, 2.0	-11.5, -0.4	-11.5, 0.5	-11.5, 3.1
- 95% CI mean	(-1.0; -0.6)	(-5.7; -4.8)	(-8.9; -8.0)	(-8.0; -6.7)
- 95% CI median	(-0.9; -0.6)	(-5.2; -4.1)	(-9.8; -9.2)	(-9.7; -8.9)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15

Table 12-32: Changes from baseline in lab-data by study day for level 3 (FAS)

Characteristic	Day2-Baseline	Day3-Baseline	Day4-Baseline	Day14-Baseline	Day28-Baseline
Haemoglobin[g/dl]					
- N	115	113	112	1	
- Mean +/- SD	-0.5+/-0.6	-0.7+/-0.7	-0.7+/-0.9	-0.4+/-.	
- Median	-0.5	-0.7	-0.6	-0.4	
- p5, p25, p75, p95	-1.7, -0.8, -0.1, 0.5	-2.0, -1.2, -0.3, 0.5	-2.2, -1.1, 0.0, 0.6	-0.4, -0.4, -0.4, -0.4	
- Min, Max	-2.4, 1.0	-2.8, 1.3	-3.9, 1.2	-0.4, -0.4	
- 95% CI mean	(-0.6; -0.4)	(-0.8; -0.5)	(-0.8; -0.5)	(.; .)	
- 95% CI median	(-0.6; -0.4)	(-0.8; -0.5)	(-0.8; -0.4)	(.; .)	
- p-Value (1)	<.0001	<.0001	<.0001	1.0000	
P. falciparum[/µl]					
- N	115	113	112	109	108
- Mean +/- SD	-17705.6+/-24992.8	-33764.4+/-26328.2	-33963.4+/-26564.0	-32079.8+/-26864.9	-28569.4+/-28894.3
- Median	-12350.0	-24000.0	-23500.0	-23000.0	-21150.0
- p5, p25, p75, p95	-68500.0, -28000.0, -3000.0, 11500.0	-88800.0, -53500.0, -13000.0, -4000.0	-89000.0, -55200.0, -13000.0, -4000.0	-89000.0, -48000.0, -12500.0, -3500.0	-78000.0, -47750.0, -11750.0, 4500.0
- Min, Max	-83500.0, 90500.0	-99700.0, -2000.0	-100000, -2000.0	-100000, 19000.0	-100000, 82000.0
- 95% CI mean	(-22322.4; -13088.7)	(-38671.8; -28857.1)	(-38937.2; -28989.5)	(-37180.3; -26979.3)	(-34081.2; -23057.7)
- 95% CI median	(-16000.0; -7000.0)	(-33950.0; -19400.0)	(-34000.0; -19500.0)	(-30700.0; -17200.0)	(-30000.0; -16700.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001
ln(P. falciparum)[/µl]					
- N	115	113	112	109	108
- Mean +/- SD	-1.1+/-1.3	-5.8+/-2.5	-9.3+/-2.1	-8.4+/-3.1	-7.2+/-4.1
- Median	-1.0	-5.0	-9.9	-9.6	-9.5
- p5, p25, p75, p95	-3.6, -1.7, -0.3, 0.5	-10.8, -7.6, -4.1, -2.9	-11.4, -10.6, -8.7, -5.0	-11.4, -10.4, -7.8, -1.4	-11.3, -10.4, -3.3, 0.3
- Min, Max	-9.3, 1.3	-11.2, -1.4	-11.5, -1.2	-11.5, 0.4	-11.5, 2.5
- 95% CI mean	(-1.4; -0.9)	(-6.2; -5.3)	(-9.7; -8.9)	(-8.9; -7.8)	(-8.0; -6.4)
- 95% CI median	(-1.2; -0.7)	(-5.5; -4.5)	(-10.0; -9.6)	(-9.9; -9.0)	(-9.7; -8.6)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test; Day14 is including Day 13-15 / Day28 is including Day 25-30

Table 12-33: Changes from baseline in lab-data by WHO-Day for level 1 (FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
Haemoglobin[g/dl]				
- N	138	138		132
- Mean +/- SD	-0.8+/-0.8	-0.8+/-0.8		-0.2+/-1.1
- Median	-0.7	-0.7		-0.2
- p5, p25, p75, p95	-2.2, -1.2, -0.4, 0.1	-2.4, -1.2, -0.4, 0.3		-2.0, -0.9, 0.4, 1.6
- Min, Max	-5.7, 0.8	-5.3, 0.8		-4.9, 3.0
- 95% CI mean	(-1.0; -0.7)	(-1.0; -0.7)		(-0.4; -0.0)
- 95% CI median	(-0.8; -0.7)	(-0.8; -0.6)		(-0.4; 0.0)
- p-Value (1)	<.0001	<.0001		0.0454
P. falciparum[/µl]				
- N	138	138	138	132
- Mean +/- SD	-32825.7+/-26207.3	-34247.5+/-25780.6	-34434.1+/-25964.1	-32186.1+/-28900.7
- Median	-26325.0	-26500.0	-26000.0	-26500.0
- p5, p25, p75, p95	-88900.0, -49000.0, -12400.0, -1500.0	-89500.0, -52600.0, -15000.0, -2800.0	-89500.0, -54000.0, -14000.0, -3300.0	-83000.0, -54950.0, -8750.0, 7000.0
- Min, Max	-97230.0, 13000.0	-97950.0, -2000.0	-98000.0, -2000.0	-98000.0, 41000.0
- 95% CI mean	(-37237.1; -28414.2)	(-38587.1; -29907.8)	(-38804.7; -30063.6)	(-37162.4; -27209.9)
- 95% CI median	(-31000.0; -20800.0)	(-33500.0; -21000.0)	(-33700.0; -21000.0)	(-33000.0; -20350.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-34: Changes from baseline in lab-data by WHO-Day for level 2 (FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline
Haemoglobin[g/dl]				
- N	145	144	1	135
- Mean +/- SD	-0.8+/-0.8	-0.8+/-0.9	-2.8+/-.	-0.3+/-1.0
- Median	-0.8	-0.7	-2.8	-0.2
- p5, p25, p75, p95	-2.2, -1.4, -0.2, 0.3	-2.6, -1.5, -0.2, 0.5	-2.8, -2.8, -2.8, -2.8	-2.0, -1.0, 0.4, 1.4
- Min, Max	-2.8, 1.3	-3.4, 1.7	-2.8, -2.8	-3.5, 2.2
- 95% CI mean	(-0.9; -0.7)	(-1.0; -0.7)	(.; .)	(-0.5; -0.1)
- 95% CI median	(-0.9; -0.6)	(-0.9; -0.5)	(.; .)	(-0.4; -0.1)
- p-Value (1)	<.0001	<.0001	1.0000	0.0041
P. falciparum[/µl]				
- N	145	145	144	136
- Mean +/- SD	-29629.4+/-24765.3	-30273.2+/-25478.3	-30970.5+/-25197.3	-27844.7+/-26548.7
- Median	-21820.0	-23500.0	-24000.0	-21250.0
- p5, p25, p75, p95	-85950.0, -44800.0, -10320.0, -2350.0	-86000.0, -46500.0, -11000.0, -2500.0	-86000.0, -46750.0, -11250.0, -2500.0	-86000.0, -44750.0, -9750.0, -1250.0
- Min, Max	-96000.0, -1400.0	-96500.0, 14000.0	-96500.0, -1200.0	-96000.0, 42000.0
- 95% CI mean	(-33694.5; -25564.2)	(-34455.3; -26091.0)	(-35121.1; -26819.9)	(-32347.0; -23342.4)
- 95% CI median	(-28950.0; -16000.0)	(-30000.0; -16000.0)	(-30500.0; -18000.0)	(-27500.0; -15000.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-35: Changes from baseline in lab-data by WHO-Day for level 3 (FAS)

Characteristic	D1-Baseline	D2-Baseline	D3-Baseline	D14-Baseline	D28-Baseline
Haemoglobin[g/dl]					
- N	113	112	1	2	
- Mean +/- SD	-0.7+/-0.7	-0.7+/-0.9	-4.0+/-.	-0.2+/-0.2	
- Median	-0.7	-0.6	-4.0	-0.2	
- p5, p25, p75, p95	-2.0, -1.2, -0.3, 0.5	-2.2, -1.1, 0.0, 0.6	-4.0, -4.0, -4.0, -4.0	-0.4, -0.4, -0.1, -0.1	
- Min, Max	-2.8, 1.3	-3.9, 1.2	-4.0, -4.0	-0.4, -0.1	
- 95% CI mean	(-0.8; -0.5)	(-0.8; -0.5)	(.; .)	(-2.2; 1.7)	
- 95% CI median	(-0.8; -0.5)	(-0.8; -0.4)	(.; .)	(-0.4; -0.1)	
- p-Value (1)	<.0001	<.0001	1.0000	0.5000	
P. falciparum[/µl]					
- N	113	112	111	99	108
- Mean +/- SD	-33764.4+/-26328.2	-33963.4+/-26564.0	-33690.5+/-26456.5	-32096.0+/-26768.9	-28569.4+/-28894.3
- Median	-24000.0	-23500.0	-23000.0	-23000.0	-21150.0
- p5, p25, p75, p95	-88800.0, -53500.0, -13000.0, -4000.0	-89000.0, -55200.0, -13000.0, -4000.0	-89000.0, -54500.0, -13000.0, -4000.0	-89800.0, -48000.0, -13000.0, -3500.0	-78000.0, -47750.0, -11750.0, 4500.0
- Min, Max	-99700.0, -2000.0	-100000, -2000.0	-100000, -2000.0	-100000, 19000.0	-100000, 82000.0
- 95% CI mean	(-38671.8; -28857.1)	(-38937.2; -28989.5)	(-38667.0; -28714.1)	(-37434.9; -26757.0)	(-34081.2; -23057.7)
- 95% CI median	(-33950.0; -19400.0)	(-34000.0; -19500.0)	(-33500.0; -19500.0)	(-30000.0; -17000.0)	(-30000.0; -16700.0)
- p-Value (1)	<.0001	<.0001	<.0001	<.0001	<.0001

(1) Wilcoxon Signed Rank Test

Table 12-36: Feverflow by study day for Level 1 / 2x daily (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14
min fever per day						
- N	72	72	69	69	69	68
- Mean +/- SD	37.3+/- 1.0	36.2+/- 0.5	36.2+/- 0.5	36.0+/- 0.5	36.0+/- 0.5	36.8+/- 0.7
- Median	37.1	36.2	36.1	36.0	36.0	36.7
- p5, p25, p75, p95	35.6, 36.6, 37.8, 39.3	35.5, 35.7, 36.6, 37.2	35.4, 35.9, 36.4, 37.3	35.2, 35.8, 36.2, 36.9	35.2, 35.8, 36.2, 36.9	36.0, 36.4, 37.1, 38.4
- Min, Max	35.5, 39.7	35.2, 37.4	35.1, 37.5	35.0, 37.8	35.0, 37.8	35.6, 39.6
mean fever per day						
- N	72	72	69	69	69	68
- Mean +/- SD	38.1+/- 0.8	37.0+/- 0.6	36.6+/- 0.5	36.4+/- 0.5	36.4+/- 0.5	36.8+/- 0.7
- Median	38.0	36.9	36.5	36.3	36.3	36.7
- p5, p25, p75, p95	37.0, 37.4, 38.7, 39.5	36.1, 36.5, 37.5, 38.0	36.0, 36.3, 36.8, 37.6	35.9, 36.1, 36.5, 37.1	35.9, 36.1, 36.5, 37.1	36.0, 36.4, 37.1, 38.4
- Min, Max	36.5, 39.9	36.0, 38.7	35.9, 38.2	35.8, 39.1	35.8, 39.1	35.6, 39.6
max fever per day						
- N	72	72	69	69	69	68
- Mean +/- SD	38.9+/- 0.8	37.9+/- 1.1	37.1+/- 0.7	36.8+/- 0.5	36.8+/- 0.5	36.8+/- 0.7
- Median	39.0	37.8	36.9	36.7	36.7	36.7
- p5, p25, p75, p95	37.6, 38.2, 39.5, 40.3	36.5, 37.0, 38.5, 39.8	36.4, 36.7, 37.2, 38.7	36.2, 36.5, 37.0, 37.5	36.2, 36.5, 37.0, 37.5	36.0, 36.4, 37.1, 38.4
- Min, Max	37.5, 41.0	36.3, 40.4	36.2, 39.4	36.0, 39.9	36.0, 39.9	35.6, 39.6

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15

Table 12-37: Feverflow by study day for Level 2 / 2x daily (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14
min fever per day						
- N	72	71	68	68	68	64
- Mean +/- SD	36.9+/- 0.8	36.3+/- 0.6	36.2+/- 0.5	36.1+/- 0.4	36.1+/- 0.4	36.5+/- 0.5
- Median	36.9	36.1	36.2	36.1	36.1	36.5
- p5, p25, p75, p95	35.5, 36.4, 37.4, 38.1	35.5, 35.9, 36.6, 37.5	35.5, 35.8, 36.4, 36.9	35.4, 35.8, 36.3, 36.7	35.4, 35.8, 36.3, 36.7	35.7, 36.2, 36.8, 37.1
- Min, Max	35.4, 38.7	35.0, 38.1	35.2, 37.7	35.0, 37.4	35.0, 37.4	35.2, 38.3
mean fever per day						
- N	72	71	68	68	68	64
- Mean +/- SD	37.8+/- 0.6	36.9+/- 0.7	36.7+/- 0.5	36.5+/- 0.3	36.5+/- 0.3	36.5+/- 0.5
- Median	37.8	36.8	36.6	36.4	36.4	36.5
- p5, p25, p75, p95	36.8, 37.4, 38.2, 38.8	36.1, 36.5, 37.3, 38.2	36.1, 36.4, 36.9, 38.0	36.0, 36.2, 36.6, 37.0	36.0, 36.2, 36.6, 37.0	35.7, 36.2, 36.8, 37.1
- Min, Max	36.7, 39.4	36.0, 38.8	36.0, 38.3	35.8, 37.5	35.8, 37.5	35.2, 38.3
max fever per day						
- N	72	71	68	68	68	64
- Mean +/- SD	38.8+/- 0.8	37.7+/- 1.0	37.2+/- 0.7	36.8+/- 0.4	36.8+/- 0.4	36.5+/- 0.5
- Median	38.9	37.5	37.1	36.8	36.8	36.5
- p5, p25, p75, p95	37.5, 38.0, 39.4, 40.1	36.5, 36.9, 38.3, 39.7	36.4, 36.8, 37.4, 38.7	36.4, 36.5, 37.0, 37.6	36.4, 36.5, 37.0, 37.6	35.7, 36.2, 36.8, 37.1
- Min, Max	37.5, 40.4	36.2, 40.2	36.3, 39.8	36.3, 38.3	36.3, 38.3	35.2, 38.3

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15

Table 12-38: Feverflow by study day for Level 3 / 2x daily (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14	Day28
min fever per day							
- N	53	53	52	51	51	50	50
- Mean +/- SD	36.7+/- 0.7	36.1+/- 0.5	36.1+/- 0.4	36.2+/- 0.4	36.2+/- 0.4	36.7+/- 0.6	36.7+/- 0.6
- Median	36.8	36.1	36.1	36.2	36.2	36.6	36.6
- p5, p25, p75, p95	35.6, 36.2, 37.2, 37.8	35.5, 35.8, 36.3, 37.0	35.4, 35.8, 36.4, 36.8	35.5, 35.9, 36.5, 36.8	35.5, 35.9, 36.5, 36.8	35.9, 36.3, 36.9, 37.8	35.9, 36.3, 36.9, 37.8
- Min, Max	35.4, 38.2	35.1, 37.2	35.2, 37.1	35.0, 36.9	35.0, 36.9	35.6, 38.3	35.6, 38.3
mean fever per day							
- N	53	53	52	51	51	50	50
- Mean +/- SD	37.7+/- 0.5	36.7+/- 0.5	36.5+/- 0.3	36.5+/- 0.4	36.5+/- 0.4	36.7+/- 0.6	36.7+/- 0.6
- Median	37.6	36.7	36.5	36.5	36.5	36.6	36.6
- p5, p25, p75, p95	37.0, 37.3, 38.0, 38.5	36.0, 36.4, 37.1, 37.6	36.1, 36.3, 36.7, 37.0	35.8, 36.3, 36.7, 37.1	35.8, 36.3, 36.7, 37.1	35.9, 36.3, 36.9, 37.8	35.9, 36.3, 36.9, 37.8
- Min, Max	36.8, 38.8	35.9, 37.9	35.9, 37.5	35.7, 37.4	35.7, 37.4	35.6, 38.3	35.6, 38.3
max fever per day							
- N	53	53	52	51	51	50	50
- Mean +/- SD	38.9+/- 0.8	37.4+/- 0.7	36.9+/- 0.3	36.8+/- 0.4	36.8+/- 0.4	36.7+/- 0.6	36.7+/- 0.6
- Median	39.0	37.3	36.9	36.8	36.8	36.6	36.6
- p5, p25, p75, p95	37.6, 38.2, 39.4, 40.1	36.3, 36.8, 37.8, 38.7	36.5, 36.7, 37.1, 37.6	36.1, 36.5, 37.1, 37.3	36.1, 36.5, 37.1, 37.3	35.9, 36.3, 36.9, 37.8	35.9, 36.3, 36.9, 37.8
- Min, Max	37.5, 40.3	36.3, 39.4	36.3, 38.1	36.0, 38.3	36.0, 38.3	35.6, 38.3	35.6, 38.3

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15
D28 is the 28th day after first drug intake, but including of day 25, 26, 27, 29, 30

Table 12-39: Feverflow by WHO-Day for Level 1 / 2x daily (FAS)

Characteristic	D0	D1	D2	D3	D14
min fever per day					
- N	72	72	69	68	64
- Mean +/- SD	36.3+/- 0.6	36.2+/- 0.6	36.0+/- 0.6	36.5+/- 0.5	36.8+/- 0.6
- Median	36.2	36.2	35.9	36.4	36.7
- p5, p25, p75, p95	35.5, 35.8, 36.7, 37.4	35.5, 35.9, 36.5, 37.5	35.2, 35.6, 36.2, 36.9	35.8, 36.2, 36.7, 37.3	36.0, 36.4, 37.1, 38.2
- Min, Max	35.2, 38.1	35.1, 37.8	35.0, 39.4	35.2, 38.1	35.6, 39.0
mean fever per day					
- N	72	72	69	68	64
- Mean +/- SD	37.2+/- 0.8	36.8+/- 0.6	36.4+/- 0.5	36.7+/- 0.4	36.8+/- 0.6
- Median	37.1	36.7	36.3	36.6	36.7
- p5, p25, p75, p95	36.2, 36.6, 37.7, 38.7	36.1, 36.4, 37.3, 38.1	35.9, 36.2, 36.5, 37.2	36.0, 36.5, 36.9, 37.4	36.0, 36.4, 37.1, 38.2
- Min, Max	35.7, 39.2	35.9, 38.7	35.8, 39.7	35.7, 38.1	35.6, 39.0
max fever per day					
- N	72	72	69	68	64
- Mean +/- SD	38.2+/- 1.1	37.6+/- 1.0	36.9+/- 0.6	36.9+/- 0.4	36.8+/- 0.6
- Median	38.2	37.3	36.8	36.9	36.7
- p5, p25, p75, p95	36.9, 37.3, 39.3, 40.1	36.6, 36.8, 38.1, 39.7	36.2, 36.5, 37.1, 37.5	36.2, 36.6, 37.1, 37.6	36.0, 36.4, 37.1, 38.2
- Min, Max	36.5, 40.5	36.3, 40.4	36.1, 39.9	35.9, 38.1	35.6, 39.0

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-40: Feverflow by WHO-Day for Level 2 / 2x daily (FAS)

Characteristic	D0	D1	D2	D3	D14
min fever per day					
- N	72	68	68	67	64
- Mean +/- SD	36.2+/- 0.6	36.2+/- 0.5	36.0+/- 0.4	36.4+/- 0.4	36.5+/- 0.5
- Median	36.1	36.1	36.0	36.4	36.5
- p5, p25, p75, p95	35.4, 35.9, 36.6, 37.5	35.5, 35.8, 36.5, 36.9	35.4, 35.7, 36.3, 36.7	35.7, 36.1, 36.6, 37.1	35.7, 36.2, 36.8, 37.1
- Min, Max	35.0, 37.5	35.2, 37.8	35.0, 37.2	35.5, 38.2	35.2, 38.3
mean fever per day					
- N	72	68	68	67	64
- Mean +/- SD	37.1+/- 0.7	36.8+/- 0.6	36.6+/- 0.4	36.6+/- 0.4	36.5+/- 0.5
- Median	36.8	36.7	36.6	36.5	36.5
- p5, p25, p75, p95	36.2, 36.6, 37.4, 38.4	36.2, 36.4, 37.2, 38.0	36.0, 36.3, 36.8, 37.4	36.0, 36.3, 36.8, 37.2	35.7, 36.2, 36.8, 37.1
- Min, Max	35.9, 38.8	36.0, 38.4	35.7, 38.0	35.9, 38.3	35.2, 38.3
max fever per day					
- N	72	68	68	67	64
- Mean +/- SD	38.0+/- 1.0	37.5+/- 0.9	37.1+/- 0.7	36.8+/- 0.4	36.5+/- 0.5
- Median	37.7	37.2	37.1	36.8	36.5
- p5, p25, p75, p95	36.8, 37.3, 38.7, 39.9	36.4, 36.9, 37.9, 39.5	36.3, 36.7, 37.4, 38.4	36.3, 36.4, 37.0, 37.5	35.7, 36.2, 36.8, 37.1
- Min, Max	36.5, 40.4	36.3, 40.2	36.1, 39.7	35.9, 38.3	35.2, 38.3

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-41: Feverflow by WHO-Day for Level 3 / 2x daily (FAS)

Characteristic	D0	D1	D2	D3	D14	D28
min fever per day						
- N	53	52	51	51	46	49
- Mean +/- SD	36.1+/- 0.5	36.1+/- 0.4	36.0+/- 0.4	36.4+/- 0.5	36.6+/- 0.5	36.6+/- 0.4
- Median	36.0	36.1	36.0	36.4	36.5	36.5
- p5, p25, p75, p95	35.4, 35.8, 36.4, 36.9	35.5, 35.8, 36.3, 36.8	35.4, 35.8, 36.3, 36.8	35.7, 36.0, 36.6, 37.0	35.9, 36.2, 36.8, 37.3	36.0, 36.3, 36.8, 37.3
- Min, Max	35.1, 37.1	35.2, 37.0	35.0, 37.3	35.3, 38.3	35.6, 38.3	35.9, 37.5
mean fever per day						
- N	53	52	51	51	46	49
- Mean +/- SD	36.9+/- 0.4	36.6+/- 0.4	36.5+/- 0.3	36.6+/- 0.4	36.6+/- 0.5	36.6+/- 0.4
- Median	36.9	36.6	36.5	36.6	36.5	36.5
- p5, p25, p75, p95	36.3, 36.7, 37.1, 37.8	36.1, 36.3, 37.0, 37.4	36.0, 36.3, 36.6, 37.1	36.0, 36.3, 36.8, 37.1	35.9, 36.2, 36.8, 37.3	36.0, 36.3, 36.8, 37.3
- Min, Max	36.1, 38.3	36.1, 37.6	35.8, 37.6	35.9, 38.4	35.6, 38.3	35.9, 37.5
max fever per day						
- N	53	52	51	51	46	49
- Mean +/- SD	37.8+/- 0.7	37.3+/- 0.7	37.0+/- 0.4	36.8+/- 0.4	36.6+/- 0.5	36.6+/- 0.4
- Median	37.8	37.1	37.0	36.8	36.5	36.5
- p5, p25, p75, p95	36.8, 37.3, 38.2, 39.1	36.4, 36.8, 37.6, 38.5	36.4, 36.7, 37.1, 37.6	36.2, 36.5, 37.0, 37.3	35.9, 36.2, 36.8, 37.3	36.0, 36.3, 36.8, 37.3
- Min, Max	36.3, 39.4	36.3, 38.7	36.0, 38.1	35.9, 38.4	35.6, 38.3	35.9, 37.5

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-42: Feverflow by study day for Level 1 / 4x daily (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14
min fever per day						
- N	75	75	71	70	70	70
- Mean +/- SD	37.1+/- 0.8	36.2+/- 0.7	36.2+/- 0.5	36.0+/- 0.5	36.0+/- 0.5	36.6+/- 0.5
- Median	37.0	36.1	36.2	36.1	36.1	36.7
- p5, p25, p75, p95	35.9, 36.5, 37.8, 38.6	35.4, 35.8, 36.4, 37.7	35.5, 35.9, 36.5, 37.1	35.2, 35.7, 36.4, 36.8	35.2, 35.7, 36.4, 36.8	35.6, 36.4, 36.9, 37.5
- Min, Max	35.5, 39.3	35.1, 38.4	35.1, 37.7	35.0, 37.3	35.0, 37.3	35.6, 38.0
mean fever per day						
- N	75	75	71	70	70	70
- Mean +/- SD	38.0+/- 0.8	37.0+/- 0.7	36.7+/- 0.5	36.5+/- 0.4	36.5+/- 0.4	36.6+/- 0.5
- Median	37.9	36.8	36.7	36.5	36.5	36.7
- p5, p25, p75, p95	37.1, 37.4, 38.5, 39.5	36.0, 36.5, 37.5, 38.3	36.0, 36.4, 37.0, 37.7	35.9, 36.2, 36.6, 37.3	35.9, 36.2, 36.6, 37.3	35.6, 36.4, 36.9, 37.5
- Min, Max	35.5, 40.0	35.6, 38.9	35.9, 38.3	35.8, 37.7	35.8, 37.7	35.6, 38.0
max fever per day						
- N	75	75	71	70	70	70
- Mean +/- SD	38.9+/- 0.9	37.7+/- 0.9	37.2+/- 0.6	36.9+/- 0.5	36.9+/- 0.5	36.6+/- 0.5
- Median	39.0	37.5	37.0	36.8	36.8	36.7
- p5, p25, p75, p95	37.6, 38.2, 39.7, 40.2	36.4, 36.9, 38.3, 39.2	36.3, 36.8, 37.4, 38.7	36.4, 36.6, 37.0, 38.1	36.4, 36.6, 37.0, 38.1	35.6, 36.4, 36.9, 37.5
- Min, Max	35.5, 40.7	35.8, 40.1	36.0, 39.0	36.3, 38.6	36.3, 38.6	35.6, 38.0

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15

Table 12-43: Feverflow by study day for Level 2 / 4x daily (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14
min fever per day						
- N	78	77	77	77	77	74
- Mean +/- SD	37.1+/- 0.8	36.3+/- 0.6	36.3+/- 0.6	36.0+/- 0.5	36.0+/- 0.5	36.7+/- 0.6
- Median	36.9	36.2	36.2	36.0	36.0	36.6
- p5, p25, p75, p95	35.8, 36.6, 37.5, 38.6	35.4, 35.9, 36.5, 37.5	35.5, 35.9, 36.8, 37.4	35.4, 35.7, 36.3, 37.1	35.4, 35.7, 36.3, 37.1	36.0, 36.3, 36.9, 37.7
- Min, Max	35.6, 39.6	35.0, 37.7	35.4, 37.9	35.1, 37.3	35.1, 37.3	35.0, 39.5
mean fever per day						
- N	78	77	77	77	77	74
- Mean +/- SD	38.0+/- 0.7	37.0+/- 0.7	36.8+/- 0.7	36.5+/- 0.5	36.5+/- 0.5	36.7+/- 0.6
- Median	37.9	36.8	36.5	36.4	36.4	36.6
- p5, p25, p75, p95	37.1, 37.5, 38.3, 39.2	36.1, 36.5, 37.4, 38.4	36.1, 36.3, 37.2, 38.2	35.9, 36.1, 36.7, 37.6	35.9, 36.1, 36.7, 37.6	36.0, 36.3, 36.9, 37.7
- Min, Max	36.8, 39.6	35.7, 39.1	35.7, 38.8	35.7, 38.1	35.7, 38.1	35.0, 39.5
max fever per day						
- N	78	77	77	77	77	74
- Mean +/- SD	39.1+/- 0.7	37.9+/- 1.2	37.2+/- 0.8	36.9+/- 0.7	36.9+/- 0.7	36.7+/- 0.6
- Median	39.1	37.6	37.0	36.8	36.8	36.6
- p5, p25, p75, p95	37.8, 38.5, 39.6, 40.1	36.5, 37.0, 38.8, 40.0	36.3, 36.7, 37.5, 38.9	36.1, 36.5, 37.2, 38.2	36.1, 36.5, 37.2, 38.2	36.0, 36.3, 36.9, 37.7
- Min, Max	37.5, 40.8	35.9, 40.4	36.3, 39.9	35.8, 39.9	35.8, 39.9	35.0, 39.5

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15

Table 12-44: Feverflow by study day for Level 3 / 4x daily (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14	Day28
min fever per day							
- N	62	62	61	61	61	60	60
- Mean +/- SD	36.7+/- 0.7	36.2+/- 0.5	36.1+/- 0.5	36.2+/- 0.4	36.2+/- 0.4	36.6+/- 0.5	36.6+/- 0.5
- Median	36.8	36.1	36.0	36.1	36.1	36.6	36.6
- p5, p25, p75, p95	35.6, 36.0, 37.2, 37.6	35.5, 35.9, 36.6, 37.1	35.5, 35.8, 36.4, 36.9	35.6, 35.9, 36.3, 36.8	35.6, 35.9, 36.3, 36.8	35.9, 36.3, 36.8, 37.5	35.9, 36.3, 36.8, 37.5
- Min, Max	35.5, 38.4	35.2, 37.7	35.2, 37.6	35.5, 36.9	35.5, 36.9	35.6, 38.7	35.6, 38.7
mean fever per day							
- N	62	62	61	61	61	60	60
- Mean +/- SD	37.5+/- 0.5	36.8+/- 0.6	36.6+/- 0.4	36.5+/- 0.3	36.5+/- 0.3	36.6+/- 0.5	36.6+/- 0.5
- Median	37.5	36.7	36.6	36.4	36.4	36.6	36.6
- p5, p25, p75, p95	36.7, 37.2, 37.8, 38.4	36.1, 36.4, 37.0, 38.0	36.1, 36.3, 36.8, 37.2	36.0, 36.2, 36.7, 37.0	36.0, 36.2, 36.7, 37.0	35.9, 36.3, 36.8, 37.5	35.9, 36.3, 36.8, 37.5
- Min, Max	36.6, 38.8	36.0, 38.3	35.8, 38.1	35.9, 37.1	35.9, 37.1	35.6, 38.7	35.6, 38.7
max fever per day							
- N	62	62	61	61	61	60	60
- Mean +/- SD	38.6+/- 0.8	37.4+/- 0.8	37.0+/- 0.5	36.8+/- 0.4	36.8+/- 0.4	36.6+/- 0.5	36.6+/- 0.5
- Median	38.6	37.2	36.9	36.8	36.8	36.6	36.6
- p5, p25, p75, p95	37.5, 38.0, 39.4, 40.1	36.5, 36.8, 38.0, 39.1	36.4, 36.7, 37.2, 37.8	36.2, 36.5, 37.1, 37.4	36.2, 36.5, 37.1, 37.4	35.9, 36.3, 36.8, 37.5	35.9, 36.3, 36.8, 37.5
- Min, Max	37.5, 40.2	36.3, 39.7	36.2, 38.9	36.1, 37.6	36.1, 37.6	35.6, 38.7	35.6, 38.7

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15
D28 is the 28th day after first drug intake, but including of day 25, 26, 27, 29, 30

Table 12-45: Feverflow by WHO-Day for Level 1 / 4x daily (FAS)

Characteristic	D0	D1	D2	D3	D14
min fever per day					
- N	75	72	70	70	69
- Mean +/- SD	36.3+/- 0.7	36.3+/- 0.5	36.0+/- 0.6	36.5+/- 0.5	36.6+/- 0.5
- Median	36.1	36.2	36.0	36.5	36.7
- p5, p25, p75, p95	35.4, 35.8, 36.7, 37.7	35.4, 35.9, 36.7, 37.2	35.1, 35.6, 36.3, 37.2	35.7, 36.2, 36.7, 37.0	35.6, 36.4, 36.9, 37.5
- Min, Max	35.1, 38.0	35.1, 37.9	35.0, 37.7	35.4, 38.6	35.6, 38.0
mean fever per day					
- N	75	72	70	70	69
- Mean +/- SD	37.1+/- 0.7	36.9+/- 0.6	36.5+/- 0.5	36.7+/- 0.5	36.6+/- 0.5
- Median	36.9	36.8	36.5	36.7	36.7
- p5, p25, p75, p95	36.1, 36.5, 37.8, 38.5	36.0, 36.4, 37.3, 38.1	35.8, 36.2, 36.7, 37.4	36.1, 36.4, 36.9, 37.3	35.6, 36.4, 36.9, 37.5
- Min, Max	35.9, 38.9	35.8, 38.4	35.5, 38.0	35.8, 39.2	35.6, 38.0
max fever per day					
- N	75	72	70	70	69
- Mean +/- SD	38.0+/- 1.0	37.6+/- 0.9	37.0+/- 0.5	36.9+/- 0.6	36.6+/- 0.5
- Median	37.8	37.4	37.0	36.8	36.7
- p5, p25, p75, p95	36.6, 37.1, 38.7, 40.0	36.4, 36.9, 38.3, 39.1	36.3, 36.7, 37.1, 38.1	36.3, 36.6, 37.0, 37.5	35.6, 36.4, 36.9, 37.5
- Min, Max	36.2, 40.4	36.0, 39.2	35.9, 38.6	35.8, 39.8	35.6, 38.0

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-46: Feverflow by WHO-Day for Level 2 / 4x daily (FAS)

Characteristic	D0	D1	D2	D3	D14
min fever per day					
- N	77	77	77	77	72
- Mean +/- SD	36.3+/- 0.6	36.3+/- 0.6	36.0+/- 0.5	36.4+/- 0.6	36.6+/- 0.5
- Median	36.2	36.2	36.0	36.3	36.6
- p5, p25, p75, p95	35.4, 35.9, 36.6, 37.5	35.5, 35.9, 36.8, 37.5	35.4, 35.7, 36.3, 37.0	35.6, 36.1, 36.7, 37.7	36.0, 36.3, 36.9, 37.7
- Min, Max	35.0, 37.9	35.4, 37.9	35.1, 37.3	35.6, 38.4	35.0, 38.6
mean fever per day					
- N	77	77	77	77	72
- Mean +/- SD	37.2+/- 0.7	36.9+/- 0.7	36.6+/- 0.5	36.7+/- 0.6	36.6+/- 0.5
- Median	37.1	36.7	36.5	36.6	36.6
- p5, p25, p75, p95	36.2, 36.6, 37.7, 38.6	36.0, 36.4, 37.5, 38.2	35.9, 36.3, 36.9, 37.5	36.0, 36.3, 36.9, 38.1	36.0, 36.3, 36.9, 37.7
- Min, Max	35.9, 38.8	35.7, 39.2	35.8, 38.0	35.9, 39.2	35.0, 38.6
max fever per day					
- N	77	77	77	77	72
- Mean +/- SD	38.2+/- 1.1	37.7+/- 1.1	37.2+/- 0.8	36.9+/- 0.6	36.6+/- 0.5
- Median	38.2	37.4	37.0	36.8	36.6
- p5, p25, p75, p95	36.7, 37.2, 39.2, 39.8	36.5, 36.9, 38.7, 40.0	36.4, 36.7, 37.4, 38.9	36.3, 36.5, 37.1, 38.2	36.0, 36.3, 36.9, 37.7
- Min, Max	36.2, 40.3	35.9, 40.4	36.1, 39.9	36.0, 39.9	35.0, 38.6

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-47: Feverflow by WHO-Day for Level 3 / 4x daily (FAS)

Characteristic	D0	D1	D2	D3	D14	D28
min fever per day						
- N	62	61	61	60	53	59
- Mean +/- SD	36.1+/- 0.5	36.1+/- 0.4	36.1+/- 0.4	36.3+/- 0.4	36.5+/- 0.5	36.6+/- 0.6
- Median	36.1	36.0	36.1	36.3	36.5	36.5
- p5, p25, p75, p95	35.5, 35.7, 36.5, 37.1	35.4, 35.8, 36.3, 36.7	35.5, 35.8, 36.3, 36.8	35.6, 36.1, 36.5, 37.0	35.9, 36.2, 36.8, 37.8	35.9, 36.2, 36.8, 37.5
- Min, Max	35.3, 37.3	35.2, 37.0	35.5, 37.1	35.5, 37.2	35.6, 38.7	35.8, 40.0
mean fever per day						
- N	62	61	61	60	53	59
- Mean +/- SD	36.9+/- 0.6	36.7+/- 0.4	36.5+/- 0.4	36.5+/- 0.3	36.5+/- 0.5	36.6+/- 0.6
- Median	36.8	36.6	36.5	36.5	36.5	36.5
- p5, p25, p75, p95	36.2, 36.5, 37.2, 37.9	36.1, 36.5, 36.9, 37.4	35.9, 36.4, 36.8, 37.2	36.0, 36.3, 36.7, 37.1	35.9, 36.2, 36.8, 37.8	35.9, 36.2, 36.8, 37.5
- Min, Max	36.0, 38.6	36.0, 37.8	35.8, 37.6	35.7, 37.3	35.6, 38.7	35.8, 40.0
max fever per day						
- N	62	61	61	60	53	59
- Mean +/- SD	37.7+/- 0.9	37.3+/- 0.7	37.0+/- 0.5	36.7+/- 0.4	36.5+/- 0.5	36.6+/- 0.6
- Median	37.6	37.2	36.9	36.8	36.5	36.5
- p5, p25, p75, p95	36.6, 37.1, 38.2, 39.3	36.5, 36.8, 37.8, 38.8	36.3, 36.7, 37.2, 37.7	36.2, 36.5, 37.0, 37.3	35.9, 36.2, 36.8, 37.8	35.9, 36.2, 36.8, 37.5
- Min, Max	36.2, 40.2	36.3, 39.1	35.8, 38.6	35.8, 37.5	35.6, 38.7	35.8, 40.0

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-48: Feverflow by study day for Level 1 (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14
min fever per day						
- N	147	147	140	139	139	138
- Mean +/- SD	37.2+/- 0.9	36.2+/- 0.6	36.2+/- 0.5	36.0+/- 0.5	36.0+/- 0.5	36.7+/- 0.6
- Median	37.0	36.2	36.2	36.0	36.0	36.7
- p5, p25, p75, p95	35.8, 36.6, 37.8, 39.2	35.4, 35.7, 36.6, 37.3	35.5, 35.9, 36.5, 37.2	35.2, 35.7, 36.3, 36.9	35.2, 35.7, 36.3, 36.9	35.8, 36.4, 37.0, 37.9
- Min, Max	35.5, 39.7	35.1, 38.4	35.1, 37.7	35.0, 37.8	35.0, 37.8	35.6, 39.6
mean fever per day						
- N	147	147	140	139	139	138
- Mean +/- SD	38.0+/- 0.8	37.0+/- 0.7	36.7+/- 0.5	36.4+/- 0.4	36.4+/- 0.4	36.7+/- 0.6
- Median	38.0	36.8	36.6	36.4	36.4	36.7
- p5, p25, p75, p95	37.1, 37.4, 38.5, 39.5	36.1, 36.5, 37.5, 38.1	36.0, 36.3, 36.9, 37.6	35.9, 36.2, 36.6, 37.3	35.9, 36.2, 36.6, 37.3	35.8, 36.4, 37.0, 37.9
- Min, Max	35.5, 40.0	35.6, 38.9	35.9, 38.3	35.8, 39.1	35.8, 39.1	35.6, 39.6
max fever per day						
- N	147	147	140	139	139	138
- Mean +/- SD	38.9+/- 0.9	37.8+/- 1.0	37.1+/- 0.7	36.8+/- 0.5	36.8+/- 0.5	36.7+/- 0.6
- Median	39.0	37.6	37.0	36.7	36.7	36.7
- p5, p25, p75, p95	37.6, 38.2, 39.6, 40.2	36.5, 36.9, 38.5, 39.6	36.3, 36.7, 37.3, 38.7	36.3, 36.5, 37.0, 37.8	36.3, 36.5, 37.0, 37.8	35.8, 36.4, 37.0, 37.9
- Min, Max	35.5, 41.0	35.8, 40.4	36.0, 39.4	36.0, 39.9	36.0, 39.9	35.6, 39.6

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15

Table 12-49: Feverflow by study day for Level 2 (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14
min fever per day						
- N	150	148	145	145	145	138
- Mean +/- SD	37.0+/- 0.8	36.3+/- 0.6	36.2+/- 0.5	36.1+/- 0.4	36.1+/- 0.4	36.6+/- 0.6
- Median	36.9	36.2	36.2	36.0	36.0	36.5
- p5, p25, p75, p95	35.6, 36.5, 37.4, 38.4	35.5, 35.9, 36.5, 37.5	35.5, 35.8, 36.6, 37.3	35.4, 35.7, 36.3, 36.9	35.4, 35.7, 36.3, 36.9	35.9, 36.2, 36.9, 37.6
- Min, Max	35.4, 39.6	35.0, 38.1	35.2, 37.9	35.0, 37.4	35.0, 37.4	35.0, 39.5
mean fever per day						
- N	150	148	145	145	145	138
- Mean +/- SD	37.9+/- 0.6	37.0+/- 0.7	36.7+/- 0.6	36.5+/- 0.4	36.5+/- 0.4	36.6+/- 0.6
- Median	37.9	36.8	36.6	36.4	36.4	36.5
- p5, p25, p75, p95	36.9, 37.4, 38.3, 39.1	36.1, 36.5, 37.3, 38.4	36.1, 36.4, 37.0, 38.0	35.9, 36.2, 36.6, 37.4	35.9, 36.2, 36.6, 37.4	35.9, 36.2, 36.9, 37.6
- Min, Max	36.7, 39.6	35.7, 39.1	35.7, 38.8	35.7, 38.1	35.7, 38.1	35.0, 39.5
max fever per day						
- N	150	148	145	145	145	138
- Mean +/- SD	38.9+/- 0.8	37.8+/- 1.1	37.2+/- 0.7	36.9+/- 0.6	36.9+/- 0.6	36.6+/- 0.6
- Median	39.0	37.5	37.1	36.8	36.8	36.5
- p5, p25, p75, p95	37.5, 38.4, 39.5, 40.1	36.5, 36.9, 38.7, 39.9	36.4, 36.7, 37.5, 38.8	36.3, 36.5, 37.1, 37.7	36.3, 36.5, 37.1, 37.7	35.9, 36.2, 36.9, 37.6
- Min, Max	37.5, 40.8	35.9, 40.4	36.3, 39.9	35.8, 39.9	35.8, 39.9	35.0, 39.5

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15

Table 12-50: Feverflow by study day for Level 3 (FAS)

Characteristic	Day1	Day2	Day3	Day4	Day5	Day14	Day28
min fever per day							
- N	115	115	113	112	112	110	110
- Mean +/- SD	36.7+/- 0.7	36.2+/- 0.5	36.1+/- 0.4	36.2+/- 0.4	36.2+/- 0.4	36.6+/- 0.5	36.6+/- 0.5
- Median	36.8	36.1	36.0	36.2	36.2	36.6	36.6
- p5, p25, p75, p95	35.6, 36.1, 37.2, 37.6	35.5, 35.8, 36.5, 37.1	35.4, 35.8, 36.4, 36.8	35.6, 35.9, 36.5, 36.8	35.6, 35.9, 36.5, 36.8	35.9, 36.3, 36.8, 37.8	35.9, 36.3, 36.8, 37.8
- Min, Max	35.4, 38.4	35.1, 37.7	35.2, 37.6	35.0, 36.9	35.0, 36.9	35.6, 38.7	35.6, 38.7
mean fever per day							
- N	115	115	113	112	112	110	110
- Mean +/- SD	37.6+/- 0.5	36.8+/- 0.5	36.6+/- 0.4	36.5+/- 0.3	36.5+/- 0.3	36.6+/- 0.5	36.6+/- 0.5
- Median	37.6	36.7	36.5	36.4	36.4	36.6	36.6
- p5, p25, p75, p95	36.8, 37.2, 38.0, 38.5	36.1, 36.4, 37.1, 37.9	36.1, 36.3, 36.8, 37.1	35.9, 36.2, 36.7, 37.1	35.9, 36.2, 36.7, 37.1	35.9, 36.3, 36.8, 37.8	35.9, 36.3, 36.8, 37.8
- Min, Max	36.6, 38.8	35.9, 38.3	35.8, 38.1	35.7, 37.4	35.7, 37.4	35.6, 38.7	35.6, 38.7
max fever per day							
- N	115	115	113	112	112	110	110
- Mean +/- SD	38.7+/- 0.8	37.4+/- 0.8	37.0+/- 0.4	36.8+/- 0.4	36.8+/- 0.4	36.6+/- 0.5	36.6+/- 0.5
- Median	38.7	37.2	36.9	36.8	36.8	36.6	36.6
- p5, p25, p75, p95	37.5, 38.0, 39.4, 40.1	36.3, 36.8, 37.8, 39.1	36.4, 36.7, 37.1, 37.7	36.1, 36.5, 37.1, 37.4	36.1, 36.5, 37.1, 37.4	35.9, 36.3, 36.8, 37.8	35.9, 36.3, 36.8, 37.8
- Min, Max	37.5, 40.3	36.3, 39.7	36.2, 38.9	36.0, 38.3	36.0, 38.3	35.6, 38.7	35.6, 38.7

min fever means the minimum of all fever measurements per calendar day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but including of day 13 and 15
D28 is the 28th day after first drug intake, but including of day 25, 26, 27, 29, 30

Table 12-51: Feverflow by WHO-Day for Level 1 (FAS)

Characteristic	D0	D1	D2	D3	D14
min fever per day					
- N	147	144	139	138	133
- Mean +/- SD	36.3+/- 0.6	36.2+/- 0.6	36.0+/- 0.6	36.5+/- 0.5	36.7+/- 0.6
- Median	36.2	36.2	35.9	36.5	36.7
- p5, p25, p75, p95	35.5, 35.8, 36.7, 37.5	35.5, 35.9, 36.6, 37.3	35.1, 35.6, 36.2, 37.1	35.8, 36.2, 36.7, 37.1	35.8, 36.4, 37.0, 37.7
- Min, Max	35.1, 38.1	35.1, 37.9	35.0, 39.4	35.2, 38.6	35.6, 39.0
mean fever per day					
- N	147	144	139	138	133
- Mean +/- SD	37.2+/- 0.8	36.9+/- 0.6	36.5+/- 0.5	36.7+/- 0.5	36.7+/- 0.6
- Median	37.0	36.8	36.4	36.7	36.7
- p5, p25, p75, p95	36.2, 36.6, 37.8, 38.5	36.1, 36.4, 37.3, 38.1	35.9, 36.2, 36.7, 37.4	36.0, 36.5, 36.9, 37.4	35.8, 36.4, 37.0, 37.7
- Min, Max	35.7, 39.2	35.8, 38.7	35.5, 39.7	35.7, 39.2	35.6, 39.0
max fever per day					
- N	147	144	139	138	133
- Mean +/- SD	38.1+/- 1.0	37.6+/- 0.9	36.9+/- 0.5	36.9+/- 0.5	36.7+/- 0.6
- Median	37.9	37.4	36.9	36.8	36.7
- p5, p25, p75, p95	36.8, 37.2, 39.0, 40.0	36.5, 36.8, 38.2, 39.2	36.2, 36.6, 37.1, 38.0	36.2, 36.6, 37.0, 37.6	35.8, 36.4, 37.0, 37.7
- Min, Max	36.2, 40.5	36.0, 40.4	35.9, 39.9	35.8, 39.8	35.6, 39.0

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-52: Feverflow by WHO-Day for Level 2 (FAS)

Characteristic	D0	D1	D2	D3	D14
min fever per day					
- N	149	145	145	144	136
- Mean +/- SD	36.3+/- 0.6	36.3+/- 0.6	36.0+/- 0.4	36.4+/- 0.5	36.6+/- 0.5
- Median	36.2	36.1	36.0	36.4	36.5
- p5, p25, p75, p95	35.4, 35.9, 36.6, 37.5	35.5, 35.8, 36.6, 37.3	35.4, 35.7, 36.3, 37.0	35.6, 36.1, 36.7, 37.2	35.9, 36.2, 36.9, 37.5
- Min, Max	35.0, 37.9	35.2, 37.9	35.0, 37.3	35.5, 38.4	35.0, 38.6
mean fever per day					
- N	149	145	145	144	136
- Mean +/- SD	37.1+/- 0.7	36.9+/- 0.7	36.6+/- 0.5	36.6+/- 0.5	36.6+/- 0.5
- Median	36.9	36.7	36.5	36.6	36.5
- p5, p25, p75, p95	36.2, 36.6, 37.6, 38.4	36.1, 36.4, 37.2, 38.2	36.0, 36.3, 36.8, 37.5	36.0, 36.3, 36.9, 37.4	35.9, 36.2, 36.9, 37.5
- Min, Max	35.9, 38.8	35.7, 39.2	35.7, 38.0	35.9, 39.2	35.0, 38.6
max fever per day					
- N	149	145	145	144	136
- Mean +/- SD	38.1+/- 1.0	37.6+/- 1.0	37.2+/- 0.7	36.9+/- 0.5	36.6+/- 0.5
- Median	37.8	37.3	37.0	36.8	36.5
- p5, p25, p75, p95	36.7, 37.2, 39.0, 39.8	36.5, 36.9, 38.2, 39.9	36.3, 36.7, 37.4, 38.4	36.3, 36.5, 37.1, 37.7	35.9, 36.2, 36.9, 37.5
- Min, Max	36.2, 40.4	35.9, 40.4	36.1, 39.9	35.9, 39.9	35.0, 38.6

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-53: Feverflow by WHO-Day for Level 3 (FAS)

Characteristic	D0	D1	D2	D3	D14	D28
min fever per day						
- N	115	113	112	111	99	108
- Mean +/- SD	36.1+/- 0.5	36.1+/- 0.4	36.1+/- 0.4	36.3+/- 0.4	36.6+/- 0.5	36.6+/- 0.5
- Median	36.0	36.1	36.1	36.3	36.5	36.5
- p5, p25, p75, p95	35.4, 35.7, 36.4, 37.1	35.5, 35.8, 36.3, 36.8	35.5, 35.8, 36.3, 36.8	35.6, 36.0, 36.6, 37.0	35.9, 36.2, 36.8, 37.8	36.0, 36.2, 36.8, 37.4
- Min, Max	35.1, 37.3	35.2, 37.0	35.0, 37.3	35.3, 38.3	35.6, 38.7	35.8, 40.0
mean fever per day						
- N	115	113	112	111	99	108
- Mean +/- SD	36.9+/- 0.5	36.7+/- 0.4	36.5+/- 0.3	36.5+/- 0.4	36.6+/- 0.5	36.6+/- 0.5
- Median	36.8	36.6	36.5	36.5	36.5	36.5
- p5, p25, p75, p95	36.2, 36.5, 37.2, 37.9	36.1, 36.4, 36.9, 37.4	35.9, 36.3, 36.7, 37.1	36.0, 36.3, 36.8, 37.1	35.9, 36.2, 36.8, 37.8	36.0, 36.2, 36.8, 37.4
- Min, Max	36.0, 38.6	36.0, 37.8	35.8, 37.6	35.7, 38.4	35.6, 38.7	35.8, 40.0
max fever per day						
- N	115	113	112	111	99	108
- Mean +/- SD	37.8+/- 0.8	37.3+/- 0.7	37.0+/- 0.4	36.8+/- 0.4	36.6+/- 0.5	36.6+/- 0.5
- Median	37.7	37.2	36.9	36.8	36.5	36.5
- p5, p25, p75, p95	36.6, 37.2, 38.2, 39.3	36.4, 36.8, 37.8, 38.7	36.4, 36.7, 37.1, 37.7	36.2, 36.5, 37.0, 37.3	35.9, 36.2, 36.8, 37.8	36.0, 36.2, 36.8, 37.4
- Min, Max	36.2, 40.2	36.3, 39.1	35.8, 38.6	35.8, 38.4	35.6, 38.7	35.8, 40.0

min fever means the minimum of all fever measurements per WHO-Day of one patient; max, mean respectively
D14 is the 14th day after first drug intake, but with tolerance of -3 and +3 calendar days

Table 12-54: Concomitant medication by generic name for Level 1 (FAS)

Medication group - generic name	2x daily (N=125)	4x daily (N=114)
Antibiotic	33(26.4%)	27(23.7%)
- Amoxicillin	9(27.3%)	3(11.1%)
- Cefadroxil	3(9.1%)	6(22.2%)
- Ciprofloxacin	1(3.0%)	0(0.0%)
- Cotrimoxazol	14(42.4%)	9(33.3%)
- Erythromycin	2(6.1%)	4(14.8%)
- Metronidazol	4(12.1%)	5(18.5%)
Antihistaminic	3(2.4%)	1(0.9%)
- Mequitazin	3(100.0%)	1(100.0%)
Antimalarial (1)	33(26.4%)	32(28.1%)
- Quinine	3(9.1%)	4(12.5%)
- Sulfadoxa/Pyrimethamin	30(90.9%)	28(87.5%)
Antipyretic	39(31.2%)	36(31.6%)
- Acetylsalicylicacid	3(7.7%)	0(0.0%)
- Ibuprofen	5(12.8%)	7(19.4%)
- Paracetamol	31(79.5%)	29(80.6%)
Others	17(13.6%)	18(15.8%)
- Albendazol	0(0.0%)	1(5.6%)
- Debridat	0(0.0%)	1(5.6%)
- Metopimazine	16(94.1%)	15(83.3%)
- Trimebutine	1(5.9%)	1(5.6%)

Number of medications taken, rather than number of patients with that specific medication, (1) apart from CQ or MB

Table 12-55: Concomitant medication by generic name for Level 2 (FAS)

Medication group - generic name	2x daily (N=116)	4x daily (N=131)
Antibiotic	24(20.7%)	32(24.4%)
- Amoxicillin	9(37.5%)	9(28.1%)
- Cefadroxil	9(37.5%)	10(31.3%)
- Ceftriaxon	1(4.2%)	0(0.0%)
- Ciprofloxacin	1(4.2%)	1(3.1%)
- Cotrimoxazol	1(4.2%)	1(3.1%)
- Erythromycin	2(8.3%)	7(21.9%)
- Gentamycin	1(4.2%)	0(0.0%)
- Metronidazol	0(0.0%)	4(12.5%)
Antihistaminic	1(0.9%)	3(2.3%)
- Mequitazin	1(100.0%)	3(100.0%)
Antimalarial (1)	35(30.2%)	28(21.4%)
- Quinine	5(14.3%)	0(0.0%)
- Sulfadoxa/Pyrimethamin	30(85.7%)	28(100.0%)
Antipyretic	26(22.4%)	47(35.9%)
- Acetylsalicylicacid	1(3.8%)	1(2.1%)
- Ibuprofen	19(73.1%)	34(72.3%)
- Paracetamol	6(23.1%)	12(25.5%)
Others	30(25.9%)	21(16.0%)
- Albendazol	3(10.0%)	1(4.8%)
- Debridat	0(0.0%)	1(4.8%)
- Diazepam	1(3.3%)	0(0.0%)
- Iron	2(6.7%)	1(4.8%)
- Metopimazine	23(76.7%)	18(85.7%)
- Phenobarbital	1(3.3%)	0(0.0%)

Number of medications taken, rather than number of patients with that specific medication, (1) apart from CQ or MB

Table 12-56: Concomitant medication by generic name for Level 3 (FAS)

Medication group - generic name	2x daily (N=80)	4x daily (N=117)
Antibiotic	16(20.0%)	33(28.2%)
- Amoxicillin	8(50.0%)	13(39.4%)
- Cefadroxil	2(12.5%)	3(9.1%)
- Ceftriaxon	0(0.0%)	1(3.0%)
- Ciprofloxacin	2(12.5%)	5(15.2%)
- Erythromycin	2(12.5%)	8(24.2%)
- Metronidazol	2(12.5%)	3(9.1%)
Antihistaminic	1(1.3%)	2(1.7%)
- Mequitazin	1(100.0%)	2(100.0%)
Antimalarial (1)	29(36.3%)	39(33.3%)
- Quinine	3(10.3%)	3(7.7%)
- Sulfadoxa/Pyrimethamin	26(89.7%)	36(92.3%)
Antipyretic	10(12.5%)	21(17.9%)
- Ibuprofen	8(80.0%)	17(81.0%)
- Paracetamol	2(20.0%)	4(19.0%)
Others	24(30.0%)	22(18.8%)
- Albendazol	3(12.5%)	2(9.1%)
- Diazepam	0(0.0%)	1(4.5%)
- Hydrocortisone	0(0.0%)	1(4.5%)
- Iron	2(8.3%)	1(4.5%)
- Metopimazine	19(79.2%)	17(77.3%)

Number of medications taken, rather than number of patients with that specific medication, (1) apart from CQ or MB

Table 12-57: Concomitant medication by generic name and group (FAS)

Medication group - generic name	2x daily (N=321)	4x daily (N=362)
Antibiotic	73(22.7%)	92(25.4%)
- Amoxicillin	26(35.6%)	25(27.2%)
- Cefadroxil	14(19.2%)	19(20.7%)
- Ceftriaxon	1(1.4%)	1(1.1%)
- Ciprofloxacin	4(5.5%)	6(6.5%)
- Cotrimoxazol	15(20.5%)	10(10.9%)
- Erythromycin	6(8.2%)	19(20.7%)
- Gentamycin	1(1.4%)	0(0.0%)
- Metronidazol	6(8.2%)	12(13.0%)
Antihistaminic	5(1.6%)	6(1.7%)
- Mequitazin	5(100.0%)	6(100.0%)
Antimalarial (1)	97(30.2%)	99(27.3%)
- Quinine	11(11.3%)	7(7.1%)
- Sulfadoxa/Pyrimethamin	86(88.7%)	92(92.9%)
Antipyretic	75(23.4%)	104(28.7%)
- Acetylsalicylicacid	4(5.3%)	1(1.0%)
- Ibuprofen	32(42.7%)	58(55.8%)
- Paracetamol	39(52.0%)	45(43.3%)
Others	71(22.1%)	61(16.9%)
- Albendazol	6(8.5%)	4(6.6%)
- Debridat	0(0.0%)	2(3.3%)
- Diazepam	1(1.4%)	1(1.6%)
- Hydrocortisone	0(0.0%)	1(1.6%)
- Iron	4(5.6%)	2(3.3%)
- Metopimazine	58(81.7%)	50(82.0%)
- Phenobarbital	1(1.4%)	0(0.0%)
- Trimebutine	1(1.4%)	1(1.6%)

Number of medications taken, rather than number of patients with that specific medication, (1) apart from CQ or MB

Table 12-58: Number of patients with concomitant medication by group and level (FAS)

Medication	level	2x daily	4x daily	Total
Antibiotic	1	28/72 (38.9%)	23/75 (30.7%)	51/147 (34.7%)
	2	20/72 (27.8%)	26/78 (33.3%)	46/150 (30.7%)
	3	15/53 (28.3%)	25/62 (40.3%)	40/115 (34.8%)
	Total	63/197 (32.0%)	74/215 (34.4%)	137/412 (33.3%)
Antihistaminic	1	2/72 (2.8%)	1/75 (1.3%)	3/147 (2.0%)
	2	1/72 (1.4%)	3/78 (3.8%)	4/150 (2.7%)
	3	1/53 (1.9%)	2/62 (3.2%)	3/115 (2.6%)
	Total	4/197 (2.0%)	6/215 (2.8%)	10/412 (2.4%)
Antimalarial	1	29/72 (40.3%)	28/75 (37.3%)	57/147 (38.8%)
	2	31/72 (43.1%)	28/78 (35.9%)	59/150 (39.3%)
	3	26/53 (49.1%)	36/62 (58.1%)	62/115 (53.9%)
	Total	86/197 (43.7%)	92/215 (42.8%)	178/412 (43.2%)
Antipyretic	1	30/72 (41.7%)	27/75 (36.0%)	57/147 (38.8%)
	2	22/72 (30.6%)	40/78 (51.3%)	62/150 (41.3%)
	3	10/53 (18.9%)	19/62 (30.6%)	29/115 (25.2%)
	Total	62/197 (31.5%)	86/215 (40.0%)	148/412 (35.9%)
Other	1	31/72 (43.1%)	36/75 (48.0%)	67/147 (45.6%)
	2	42/72 (58.3%)	36/78 (46.2%)	78/150 (52.0%)
	3	31/53 (58.5%)	29/62 (46.8%)	60/115 (52.2%)
	Total	104/197 (52.8%)	101/215 (47.0%)	205/412 (49.8%)

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Table 12-59: Primary analysis by study day for Level 1 (FAS)

Characteristic	2x daily (N=72)	4x daily (N=75)	Comparison (N=147)
RAE			
- Yes	0(0.0%)	0(0.0%)	
- No	72(100.0%)	75(100.0%)	
SAE			
- Yes	0(0.0%)	0(0.0%)	
- No	72(100.0%)	75(100.0%)	
Changes in HB[g/dl] (3)			
- N	68	70	
- Mean +/- SD	-0.8+/- 0.7	-0.8+/- 0.9	-0.0+/- 0.8
- Median	-0.8	-0.7	
- Min, Max	-3.5, 0.8	-5.3, 0.8	
- p5, p25, p75, p95	-1.7, -1.3, -0.5, 0.3	-2.4, -1.2, -0.2, 0.2	
- 95% CI mean			[-0.29; 0.26]
- p-Value (4)			0.4071

(1) CI=95% confidence interval of the rates or 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

Table 12-60: Primary analysis by study day for Level 2 (FAS)

Characteristic	2x daily (N=72)	4x daily (N=78)	Comparison (N=150)
RAE			
- Yes	1(1.4%)	1(1.3%)	
- No	71(98.6%)	77(98.7%)	
SAE			
- Yes	1(1.4%)	1(1.3%)	
- No	71(98.6%)	77(98.7%)	
- 95% CI (1)	[0.00; 0.07]	[0.00; 0.07]	[0.069; 17.00]
p-Value (2)			0.9545
Changes in HB[g/dl] (3)			
- N	67	77	
- Mean +/- SD	-0.7+/- 0.9	-1.0+/- 1.0	0.3+/- 0.9
- Median	-0.5	-1.0	
- Min, Max	-2.7, 1.2	-3.4, 1.7	
- p5, p25, p75, p95	-2.6, -1.3, -0.2, 0.5	-2.8, -1.6, -0.2, 0.5	
- 95% CI mean			[-0.01; 0.61]
- p-Value (4)			0.0465

(1) CI=95% confidence interval of the rates or 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

Table 12-61: Primary analysis by study day for Level 3 (FAS)

Characteristic	2x daily (N=53)	4x daily (N=62)	Comparison (N=115)
RAE			
- Yes	0(0.0%)	1(1.6%)	
- No	53(100.0%)	61(98.4%)	
SAE			
- Yes	0(0.0%)	1(1.6%)	
- No	53(100.0%)	61(98.4%)	
- 95% CI (1)	[0.00; 0.10]	[0.00; 0.09]	[0.016; 9.351]
p-Value (2)			0.353
Changes in HB[g/dl] (3)			
- N	51	61	
- Mean +/- SD	-0.7+/- 0.8	-0.6+/- 0.9	-0.1+/- 0.9
- Median	-0.7	-0.6	
- Min, Max	-2.8, 1.2	-3.9, 1.1	
- p5, p25, p75, p95	-2.2, -1.2, -0.2, 0.4	-1.8, -1.1, 0.1, 0.6	
- 95% CI mean			[-0.44; 0.23]
- p-Value (4)			0.3050

(1) CI=95% confidence interval of the rates or 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

Table 12-62: Primary analysis by study day for all Levels (FAS)

Characteristic	2x daily (N=197)	4x daily (N=215)	Comparison (N=412)
RAE			
- Yes	1(0.5%)	2(0.9%)	
- No	196(99.5%)	213(99.1%)	
SAE			
- Yes	1(0.5%)	2(0.9%)	
- No	196(99.5%)	213(99.1%)	
- 95% CI (1)	[0.00; 0.03]	[0.00; 0.03]	[0.050; 5.971]
p-Value (2)			0.6142
Changes in HB[g/dl] (3)			
- N	186	208	
- Mean +/- SD	-0.7+/- 0.8	-0.8+/- 0.9	0.1+/- 0.9
- Median	-0.7	-0.7	
- Min, Max	-3.5, 1.2	-5.3, 1.7	
- p5, p25, p75, p95	-2.2, -1.2, -0.3, 0.4	-2.4, -1.3, -0.1, 0.5	
- 95% CI mean			[-0.10; 0.25]
- p-Value (4)			0.7186

(1) CI=95% confidence interval of the rates or 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

Table 12-63: Primary analysis by WHO Day for Level 1 (FAS)

Characteristic	2x daily (N=72)	4x daily (N=75)	Comparison (N=147)
RAE			
- Yes	0(0.0%)	0(0.0%)	
- No	72(100.0%)	75(100.0%)	
SAE			
- Yes	0(0.0%)	0(0.0%)	
- No	72(100.0%)	75(100.0%)	
Changes in HB[g/dl] (3)			
- N	68	70	
- Mean +/- SD	-0.8+/- 0.7	-0.8+/- 0.9	-0.0+/- 0.8
- Median	-0.8	-0.7	
- Min, Max	-3.5, 0.8	-5.3, 0.8	
- p5, p25, p75, p95	-1.7, -1.3, -0.5, 0.3	-2.4, -1.2, -0.2, 0.2	
- 95% CI mean			[-0.29; 0.26]
- p-Value (4)			0.4071

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

Table 12-64: Primary analysis by WHO Day for Level 2 (FAS)

Characteristic	2x daily (N=72)	4x daily (N=78)	Comparison (N=150)
RAE			
- Yes	1(1.4%)	1(1.3%)	
- No	71(98.6%)	77(98.7%)	
SAE			
- Yes	1(1.4%)	1(1.3%)	
- No	71(98.6%)	77(98.7%)	
- 95% CI (1)	[0.00; 0.07]	[0.00; 0.07]	[0.069; 17.00]
p-Value (2)			0.9545
Changes in HB[g/dl] (3)			
- N	67	77	
- Mean +/- SD	-0.7+/- 0.9	-1.0+/- 1.0	0.3+/- 0.9
- Median	-0.5	-1.0	
- Min, Max	-2.7, 1.2	-3.4, 1.7	
- p5, p25, p75, p95	-2.6, -1.3, -0.2, 0.5	-2.8, -1.6, -0.2, 0.5	
- 95% CI mean			[-0.01; 0.61]
- p-Value (4)			0.0465

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

Table 12-65: Primary analysis by WHO Day for Level 3 (FAS)

Characteristic	2x daily (N=53)	4x daily (N=62)	Comparison (N=115)
RAE			
- Yes	0(0.0%)	1(1.6%)	
- No	53(100.0%)	61(98.4%)	
SAE			
- Yes	0(0.0%)	1(1.6%)	
- No	53(100.0%)	61(98.4%)	
- 95% CI (1)	[0.00; 0.10]	[0.00; 0.09]	[0.016; 9.351]
p-Value (2)			0.353
Changes in HB[g/dl] (3)			
- N	51	61	
- Mean +/- SD	-0.7+/- 0.8	-0.6+/- 0.9	-0.1+/- 0.9
- Median	-0.7	-0.6	
- Min, Max	-2.8, 1.2	-3.9, 1.1	
- p5, p25, p75, p95	-2.2, -1.2, -0.2, 0.4	-1.8, -1.1, 0.1, 0.6	
- 95% CI mean			[-0.44; 0.23]
- p-Value (4)			0.3050

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

Table 12-66: Primary analysis by WHO Day for all Levels (FAS)

Characteristic	2x daily (N=197)	4x daily (N=215)	Comparison (N=412)
RAE			
- Yes	1(0.5%)	2(0.9%)	
- No	196(99.5%)	213(99.1%)	
SAE			
- Yes	1(0.5%)	2(0.9%)	
- No	196(99.5%)	213(99.1%)	
- 95% CI (1)	[0.00; 0.03]	[0.00; 0.03]	[0.050; 5.971]
p-Value (2)			0.6142
Changes in HB[g/dl] (3)			
- N	186	208	
- Mean +/- SD	-0.7+/- 0.8	-0.8+/- 0.9	0.1+/- 0.9
- Median	-0.7	-0.7	
- Min, Max	-3.5, 1.2	-5.3, 1.7	
- p5, p25, p75, p95	-2.2, -1.2, -0.3, 0.4	-2.4, -1.3, -0.1, 0.5	
- 95% CI mean			[-0.10; 0.25]
- p-Value (4)			0.7186

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

Table 12-67: Efficacy results by group and dose level (PP)

	2x daily	4x daily	Group comparison
Level1 MB 36 mg/kg			
- ETF/N	1.6%, 1/62	3.0%, 2/66	p=0.5923 (1)
- LCF14/N	8.1%, 5/62	3.0%, 2/66	p=0.2047 (1)
- TF14/N	9.7%, 6/62	6.1%, 4/66	p=0.4452 (1)
- LPF14/N	24.2%, 15/62	22.7%, 15/66	p=0.8449 (1)
Level2 MB 54 mg/kg			
- ETF/N	3.1%, 2/64	6.9%, 5/73	p=0.3140 (1)
- LCF14/N	4.7%, 3/64	11.0%, 8/73	p=0.1688 (1)
- TF14/N	7.8%, 5/64	17.8%, 13/73	p=0.0783 (1)
- LPF14/N	35.9%, 23/64	17.8%, 13/73	p=0.0159 (1)
Level3 MB 72 mg/kg			
- ETF/N	0.0%, 0/47	0.0%, 0/52	-
- LCF14/N	10.6%, 5/47	9.6%, 5/52	p=0.8661 (1)
- TF14/N	10.6%, 5/47	9.6%, 5/52	p=0.8661 (1)
- LPF14/N	21.3%, 10/47	19.2%, 10/52	p=0.8002 (1)
Level comparison			
- p-value (ETF)	0.3266 (2)	0.0595 (2)	0.7290 (3), 0.0960 (4), 0.9930 (5)
- p-value (LCF14)	0.4824 (2)	0.1492 (2)	0.3168 (3), 0.2613 (4), 0.1722 (5)
- p-value (LF14)	0.8684 (2)	0.0838 (2)	0.2944 (3), 0.2634 (4), 0.1984 (5)
- p-value (LPF14)	0.1764 (2)	0.7631 (2)	0.1155 (3), 0.4045 (4), 0.2486 (5)

ETF=early treatment failure, LCF14=late clinical failure (day 14),
TF14=treatment failure (ETF or LCF14),
LPF14=late parasitological failure (day 14),
(1) group comparisons within level, (2) level comparison within group,
(3) test of overall group comparison, (4) test of overall level comparison,
(5) test of group*level interaction, Likelihood ratio tests were used
(3) and (4) also used the model with interaction term (!) and therefore a bit different from the results given in the report,
table created by t_paper_resi.sas for the publication

Table 12-68: Treatment failure by group for Level 1 (FAS)

	2x daily (N=72)	4x daily (N=75)	Total (N=147)
ETF	5(6.9%)	7(9.3%)	12(8.2%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	1(20.0%)	1(14.3%)	2(16.7%)
- reason3+4	0(0.0%)	1(14.3%)	1(8.3%)
- reason4	0(0.0%)	0(0.0%)	0(0.0%)
- reason5	4(80.0%)	5(71.4%)	9(75.0%)
LCF_14	10(13.9%)	6(8.0%)	16(10.9%)
- reason1	5(50.0%)	2(33.3%)	7(43.8%)
- reason2	2(20.0%)	3(50.0%)	5(31.3%)
- reason3	3(30.0%)	1(16.7%)	4(25.0%)
TF_14	15(20.8%)	13(17.3%)	28(19.0%)
- ETF	5(33.3%)	7(53.8%)	12(42.9%)
- LCF_14	10(66.7%)	6(46.2%)	16(57.1%)
LPF_14	16(22.2%)	15(20.0%)	31(21.1%)
- reason1	15(93.8%)	15(100.0%)	30(96.8%)
- reason2	1(6.3%)	0(0.0%)	1(3.2%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-69: Treatment failure by group for Level 2 (FAS)

	2x daily (N=72)	4x daily (N=78)	Total (N=150)
ETF	7(9.7%)	6(7.7%)	13(8.7%)
- reason1	1(14.3%)	0(0.0%)	1(7.7%)
- reason2	0(0.0%)	1(16.7%)	1(7.7%)
- reason2+3	1(14.3%)	0(0.0%)	1(7.7%)
- reason3	1(14.3%)	2(33.3%)	3(23.1%)
- reason3+4	0(0.0%)	0(0.0%)	0(0.0%)
- reason4	0(0.0%)	2(33.3%)	2(15.4%)
- reason5	4(57.1%)	1(16.7%)	5(38.5%)
LCF_14	6(8.3%)	12(15.4%)	18(12.0%)
- reason1	3(50.0%)	8(66.7%)	11(61.1%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	3(50.0%)	4(33.3%)	7(38.9%)
TF_14	13(18.1%)	18(23.1%)	31(20.7%)
- ETF	7(53.8%)	6(33.3%)	13(41.9%)
- LCF_14	6(46.2%)	12(66.7%)	18(58.1%)
LPF_14	23(31.9%)	13(16.7%)	36(24.0%)
- reason1	23(100.0%)	13(100.0%)	36(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-70: Treatment failure by group for Level 3 (FAS)

	2x daily (N=53)	4x daily (N=62)	Total (N=115)
ETF	2(3.8%)	2(3.2%)	4(3.5%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	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	2(100.0%)	2(100.0%)	4(100.0%)
LCF_14	9(17.0%)	12(19.4%)	21(18.3%)
- reason1	5(55.6%)	5(41.7%)	10(47.6%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	4(44.4%)	7(58.3%)	11(52.4%)
TF_14	11(20.8%)	14(22.6%)	25(21.7%)
- ETF	2(18.2%)	2(14.3%)	4(16.0%)
- LCF_14	9(81.8%)	12(85.7%)	21(84.0%)
LPF_14	10(18.9%)	10(16.1%)	20(17.4%)
- reason1	10(100.0%)	10(100.0%)	20(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
LCF_28	10(18.9%)	18(29.0%)	28(24.3%)
- reason1	9(90.0%)	12(66.7%)	21(75.0%)
- reason2	1(10.0%)	5(27.8%)	6(21.4%)
- reason3	0(0.0%)	1(5.6%)	1(3.6%)
TF_28	12(22.6%)	20(32.3%)	32(27.8%)
- TF_14	11(91.7%)	14(70.0%)	25(78.1%)
- LCF_28 (1)	1(8.3%)	6(30.0%)	7(21.9%)
LPF_28	21(39.6%)	23(37.1%)	44(38.3%)
- reason1	21(100.0%)	23(100.0%)	44(100.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

LCF_28-reason1: LCF_14; reason2:Fever(>=37,5°C) and parasitaemia >0 on D18-D28(WHO); reason3: Missin information

(1) without previously meeting any of the criteria of LCF_14

Table 12-71: Treatment failure by group for all Levels (FAS)

	2x daily (N=197)	4x daily (N=215)	Total (N=412)
ETF	14(7.1%)	15(7.0%)	29(7.0%)
- reason1	1(7.1%)	0(0.0%)	1(3.4%)
- reason2	0(0.0%)	1(6.7%)	1(3.4%)
- reason2+3	1(7.1%)	0(0.0%)	1(3.4%)
- reason3	2(14.3%)	3(20.0%)	5(17.2%)
- reason3+4	0(0.0%)	1(6.7%)	1(3.4%)
- reason4	0(0.0%)	2(13.3%)	2(6.9%)
- reason5	10(71.4%)	8(53.3%)	18(62.1%)
LCF_14	25(12.7%)	30(14.0%)	55(13.3%)
- reason1	13(52.0%)	15(50.0%)	28(50.9%)
- reason2	2(8.0%)	3(10.0%)	5(9.1%)
- reason3	10(40.0%)	12(40.0%)	22(40.0%)
TF_14	39(19.8%)	45(20.9%)	84(20.4%)
- ETF	14(35.9%)	15(33.3%)	29(34.5%)
- LCF_14	25(64.1%)	30(66.7%)	55(65.5%)
LPF_14	49(24.9%)	38(17.7%)	87(21.1%)
- reason1	48(98.0%)	38(100.0%)	86(98.9%)
- reason2	1(2.0%)	0(0.0%)	1(1.1%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-72: Treatment failure by group for Level 1 (PP)

	2x daily (N=62)	4x daily (N=66)	Total (N=128)
ETF	1(1.6%)	2(3.0%)	3(2.3%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	1(100.0%)	1(50.0%)	2(66.7%)
- reason3+4	0(0.0%)	1(50.0%)	1(33.3%)
- reason4	0(0.0%)	0(0.0%)	0(0.0%)
- reason5	0(0.0%)	0(0.0%)	0(0.0%)
LCF_14	5(8.1%)	2(3.0%)	7(5.5%)
- reason1	5(100.0%)	2(100.0%)	7(100.0%)
- reason3	0(0.0%)	0(0.0%)	0(0.0%)
TF_14	6(9.7%)	4(6.1%)	10(7.8%)
- ETF	1(16.7%)	2(50.0%)	3(30.0%)
- LCF_14	5(83.3%)	2(50.0%)	7(70.0%)
LPF_14	15(24.2%)	15(22.7%)	30(23.4%)
- reason1	15(100.0%)	15(100.0%)	30(100.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO); reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0

Table 12-73: Treatment failure by group for Level 2 (PP)

	2x daily (N=64)	4x daily (N=73)	Total (N=137)
ETF	2(3.1%)	5(6.8%)	7(5.1%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	1(20.0%)	1(14.3%)
- reason2+3	1(50.0%)	0(0.0%)	1(14.3%)
- reason3	1(50.0%)	2(40.0%)	3(42.9%)
- reason3+4	0(0.0%)	0(0.0%)	0(0.0%)
- reason4	0(0.0%)	2(40.0%)	2(28.6%)
- reason5	0(0.0%)	0(0.0%)	0(0.0%)
LCF_14	3(4.7%)	8(11.0%)	11(8.0%)
- reason1	3(100.0%)	8(100.0%)	11(100.0%)
- reason3	0(0.0%)	0(0.0%)	0(0.0%)
TF_14	5(7.8%)	13(17.8%)	18(13.1%)
- ETF	2(40.0%)	5(38.5%)	7(38.9%)
- LCF_14	3(60.0%)	8(61.5%)	11(61.1%)
LPF_14	23(35.9%)	13(17.8%)	36(26.3%)
- reason1	23(100.0%)	13(100.0%)	36(100.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO); reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0

Table 12-74: Treatment failure by group for Level 3 (PP)

	2x daily (N=47)	4x daily (N=52)	Total (N=99)
ETF	0(0.0%)	0(0.0%)	0(0.0%)
LCF_14	5(10.6%)	5(9.6%)	10(10.1%)
- reason1	5(100.0%)	5(100.0%)	10(100.0%)
- reason3	0(0.0%)	0(0.0%)	0(0.0%)
TF_14	5(10.6%)	5(9.6%)	10(10.1%)
- ETF	0(0.0%)	0(0.0%)	0(0.0%)
- LCF_14	5(100.0%)	5(100.0%)	10(100.0%)
LPF_14	10(21.3%)	10(19.2%)	20(20.2%)
- reason1	10(100.0%)	10(100.0%)	20(100.0%)
LCF_28	6(12.8%)	10(19.2%)	16(16.2%)
- reason1	5(83.3%)	5(50.0%)	10(62.5%)
- reason2	1(16.7%)	5(50.0%)	6(37.5%)
TF_28	6(12.8%)	10(19.2%)	16(16.2%)
- TF_14	5(83.3%)	5(50.0%)	10(62.5%)
- LCF_28 (1)	1(16.7%)	5(50.0%)	6(37.5%)
LPF_28	21(44.7%)	23(44.2%)	44(44.4%)
- reason1	21(100.0%)	23(100.0%)	44(100.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO); reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0

LCF_28-reason1: LCF_14; reason2:Fever(>=37,5°C) and parasitaemia >0 on D18-D28(WHO); reason3: Missin information

(1) without previously meeting any of the criteria of LCF_14

Table 12-75: Treatment failure by group for all Levels (PP)

	2x daily (N=173)	4x daily (N=191)	Total (N=364)
ETF	3(1.7%)	7(3.7%)	10(2.7%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	1(14.3%)	1(10.0%)
- reason2+3	1(33.3%)	0(0.0%)	1(10.0%)
- reason3	2(66.7%)	3(42.9%)	5(50.0%)
- reason3+4	0(0.0%)	1(14.3%)	1(10.0%)
- reason4	0(0.0%)	2(28.6%)	2(20.0%)
- reason5	0(0.0%)	0(0.0%)	0(0.0%)
LCF_14	13(7.5%)	15(7.9%)	28(7.7%)
- reason1	13(100.0%)	15(100.0%)	28(100.0%)
- reason3	0(0.0%)	0(0.0%)	0(0.0%)
TF_14	16(9.2%)	22(11.5%)	38(10.4%)
- ETF	3(18.8%)	7(31.8%)	10(26.3%)
- LCF_14	13(81.3%)	15(68.2%)	28(73.7%)
LPF_14	48(27.7%)	38(19.9%)	86(23.6%)
- reason1	48(100.0%)	38(100.0%)	86(100.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO); reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0

Table 12-76: Treatment failure by group for children < 2 years / Level 1 (FAS)

	2x daily (N=24)	4x daily (N=30)	Total (N=54)
ETF	1(4.2%)	3(10.0%)	4(7.4%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	1(100.0%)	0(0.0%)	1(25.0%)
- 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%)	3(100.0%)	3(75.0%)
LCF_14	5(20.8%)	1(3.3%)	6(11.1%)
- reason1	3(60.0%)	0(0.0%)	3(50.0%)
- reason2	1(20.0%)	1(100.0%)	2(33.3%)
- reason3	1(20.0%)	0(0.0%)	1(16.7%)
TF_14	6(25.0%)	4(13.3%)	10(18.5%)
- ETF	1(16.7%)	3(75.0%)	4(40.0%)
- LCF_14	5(83.3%)	1(25.0%)	6(60.0%)
LPF_14	4(16.7%)	5(16.7%)	9(16.7%)
- reason1	3(75.0%)	5(100.0%)	8(88.9%)
- reason2	1(25.0%)	0(0.0%)	1(11.1%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-77: Treatment failure by group for children < 2 years / Level 2 (FAS)

	2x daily (N=18)	4x daily (N=24)	Total (N=42)
ETF	3(16.7%)	3(12.5%)	6(14.3%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	1(33.3%)	1(33.3%)	2(33.3%)
- reason3+4	0(0.0%)	0(0.0%)	0(0.0%)
- reason4	0(0.0%)	1(33.3%)	1(16.7%)
- reason5	2(66.7%)	1(33.3%)	3(50.0%)
LCF_14	3(16.7%)	4(16.7%)	7(16.7%)
- reason1	2(66.7%)	2(50.0%)	4(57.1%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	1(33.3%)	2(50.0%)	3(42.9%)
TF_14	6(33.3%)	7(29.2%)	13(31.0%)
- ETF	3(50.0%)	3(42.9%)	6(46.2%)
- LCF_14	3(50.0%)	4(57.1%)	7(53.8%)
LPF_14	6(33.3%)	4(16.7%)	10(23.8%)
- reason1	6(100.0%)	4(100.0%)	10(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-78: Treatment failure by group for children < 2 years / Level 3 (FAS)

	2x daily (N=6)	4x daily (N=16)	Total (N=22)
ETF	0(0.0%)	1(6.3%)	1(4.5%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	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%)	1(100.0%)	1(100.0%)
LCF_14	1(16.7%)	2(12.5%)	3(13.6%)
- reason1	1(100.0%)	1(50.0%)	2(66.7%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	0(0.0%)	1(50.0%)	1(33.3%)
TF_14	1(16.7%)	3(18.8%)	4(18.2%)
- ETF	0(0.0%)	1(33.3%)	1(25.0%)
- LCF_14	1(100.0%)	2(66.7%)	3(75.0%)
LPF_14	2(33.3%)	1(6.3%)	3(13.6%)
- reason1	2(100.0%)	1(100.0%)	3(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
LCF_28	1(16.7%)	4(25.0%)	5(22.7%)
- reason1	1(100.0%)	2(50.0%)	3(60.0%)
- reason2	0(0.0%)	1(25.0%)	1(20.0%)
- reason3	0(0.0%)	1(25.0%)	1(20.0%)
TF_28	1(16.7%)	5(31.3%)	6(27.3%)
- TF_14	1(100.0%)	3(60.0%)	4(66.7%)
- LCF_28 (1)	2(40.0%)	2(33.3%)	
LPF_28	2(33.3%)	6(37.5%)	8(36.4%)
- reason1	2(100.0%)	6(100.0%)	8(100.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

LCF_28-reason1: LCF_14; reason2:Fever(>=37,5°C) and parasitaemia >0 on D18-D28(WHO); reason3: Missin information

(1) without previously meeting any of the criteria of LCF_14

Table 12-79: Treatment failure by group for children < 2 years / all Levels (FAS)

	2x daily (N=48)	4x daily (N=70)	Total (N=118)
ETF	4(8.3%)	7(10.0%)	11(9.3%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	2(50.0%)	1(14.3%)	3(27.3%)
- reason3+4	0(0.0%)	0(0.0%)	0(0.0%)
- reason4	0(0.0%)	1(14.3%)	1(9.1%)
- reason5	2(50.0%)	5(71.4%)	7(63.6%)
LCF_14	9(18.8%)	7(10.0%)	16(13.6%)
- reason1	6(66.7%)	3(42.9%)	9(56.3%)
- reason2	1(11.1%)	1(14.3%)	2(12.5%)
- reason3	2(22.2%)	3(42.9%)	5(31.3%)
TF_14	13(27.1%)	14(20.0%)	27(22.9%)
- ETF	4(30.8%)	7(50.0%)	11(40.7%)
- LCF_14	9(69.2%)	7(50.0%)	16(59.3%)
LPF_14	12(25.0%)	10(14.3%)	22(18.6%)
- reason1	11(91.7%)	10(100.0%)	21(95.5%)
- reason2	1(8.3%)	0(0.0%)	1(4.5%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-80: Treatment failure by group for children >= 2 years / Level 1 (FAS)

	2x daily (N=48)	4x daily (N=45)	Total (N=93)
ETF	4(8.3%)	4(8.9%)	8(8.6%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	0(0.0%)	1(25.0%)	1(12.5%)
- reason3+4	0(0.0%)	1(25.0%)	1(12.5%)
- reason4	0(0.0%)	0(0.0%)	0(0.0%)
- reason5	4(100.0%)	2(50.0%)	6(75.0%)
LCF_14	5(10.4%)	5(11.1%)	10(10.8%)
- reason1	2(40.0%)	2(40.0%)	4(40.0%)
- reason2	1(20.0%)	2(40.0%)	3(30.0%)
- reason3	2(40.0%)	1(20.0%)	3(30.0%)
TF_14	9(18.8%)	9(20.0%)	18(19.4%)
- ETF	4(44.4%)	4(44.4%)	8(44.4%)
- LCF_14	5(55.6%)	5(55.6%)	10(55.6%)
LPF_14	12(25.0%)	10(22.2%)	22(23.7%)
- reason1	12(100.0%)	10(100.0%)	22(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-81: Treatment failure by group for children >= 2 years / Level 2 (FAS)

	2x daily (N=54)	4x daily (N=54)	Total (N=108)
ETF	4(7.4%)	3(5.6%)	7(6.5%)
- reason1	1(25.0%)	0(0.0%)	1(14.3%)
- reason2	0(0.0%)	1(33.3%)	1(14.3%)
- reason2+3	1(25.0%)	0(0.0%)	1(14.3%)
- reason3	0(0.0%)	1(33.3%)	1(14.3%)
- reason3+4	0(0.0%)	0(0.0%)	0(0.0%)
- reason4	0(0.0%)	1(33.3%)	1(14.3%)
- reason5	2(50.0%)	0(0.0%)	2(28.6%)
LCF_14	3(5.6%)	8(14.8%)	11(10.2%)
- reason1	1(33.3%)	6(75.0%)	7(63.6%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	2(66.7%)	2(25.0%)	4(36.4%)
TF_14	7(13.0%)	11(20.4%)	18(16.7%)
- ETF	4(57.1%)	3(27.3%)	7(38.9%)
- LCF_14	3(42.9%)	8(72.7%)	11(61.1%)
LPF_14	17(31.5%)	9(16.7%)	26(24.1%)
- reason1	17(100.0%)	9(100.0%)	26(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-82: Treatment failure by group for children >= 2 years / Level 3 (FAS)

	2x daily (N=47)	4x daily (N=46)	Total (N=93)
ETF	2(4.3%)	1(2.2%)	3(3.2%)
- reason1	0(0.0%)	0(0.0%)	0(0.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason2+3	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	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	2(100.0%)	1(100.0%)	3(100.0%)
LCF_14	8(17.0%)	10(21.7%)	18(19.4%)
- reason1	4(50.0%)	4(40.0%)	8(44.4%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
- reason3	4(50.0%)	6(60.0%)	10(55.6%)
TF_14	10(21.3%)	11(23.9%)	21(22.6%)
- ETF	2(20.0%)	1(9.1%)	3(14.3%)
- LCF_14	8(80.0%)	10(90.9%)	18(85.7%)
LPF_14	8(17.0%)	9(19.6%)	17(18.3%)
- reason1	8(100.0%)	9(100.0%)	17(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)
LCF_28	9(19.1%)	14(30.4%)	23(24.7%)
- reason1	8(88.9%)	10(71.4%)	18(78.3%)
- reason2	1(11.1%)	4(28.6%)	5(21.7%)
- reason3	0(0.0%)	0(0.0%)	0(0.0%)
TF_28	11(23.4%)	15(32.6%)	26(28.0%)
- TF_14	10(90.9%)	11(73.3%)	21(80.8%)
- LCF_28 (1)	1(9.1%)	4(26.7%)	5(19.2%)
LPF_28	19(40.4%)	17(37.0%)	36(38.7%)
- reason1	19(100.0%)	17(100.0%)	36(100.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

LCF_28-reason1: LCF_14; reason2:Fever(>=37,5°C) and parasitaemia >0 on D18-D28(WHO); reason3: Missin information

(1) without previously meeting any of the criteria of LCF_14

Table 12-83: Treatment failure by group for children >= 2 years / all Levels (FAS)

	2x daily (N=149)	4x daily (N=145)	Total (N=294)
ETF	10(6.7%)	8(5.5%)	18(6.1%)
- reason1	1(10.0%)	0(0.0%)	1(5.6%)
- reason2	0(0.0%)	1(12.5%)	1(5.6%)
- reason2+3	1(10.0%)	0(0.0%)	1(5.6%)
- reason3	0(0.0%)	2(25.0%)	2(11.1%)
- reason3+4	0(0.0%)	1(12.5%)	1(5.6%)
- reason4	0(0.0%)	1(12.5%)	1(5.6%)
- reason5	8(80.0%)	3(37.5%)	11(61.1%)
LCF_14	16(10.7%)	23(15.9%)	39(13.3%)
- reason1	7(43.8%)	12(52.2%)	19(48.7%)
- reason2	1(6.3%)	2(8.7%)	3(7.7%)
- reason3	8(50.0%)	9(39.1%)	17(43.6%)
TF_14	26(17.4%)	31(21.4%)	57(19.4%)
- ETF	10(38.5%)	8(25.8%)	18(31.6%)
- LCF_14	16(61.5%)	23(74.2%)	39(68.4%)
LPF_14	37(24.8%)	28(19.3%)	65(22.1%)
- reason1	37(100.0%)	28(100.0%)	65(100.0%)
- reason2	0(0.0%)	0(0.0%)	0(0.0%)

percentages of ETF, LCF_14, TF_14 and LPF_14 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

LCF_14-reason1: reason1: Fever(>=37,5°C) and parasitaemia >0 on D4-D14(WHO)

LCF_14-reason2: treated (D4-D13) with antimalarials although no fever and/or no parasites; reason3: Missing Information

LPF_14-reason1: Temperature < 37,5°C on D14(WHO) and parasitaemia > 0; reason2: Missing Information

Table 12-84: Early treatment failures with two-sided 95% CI by group and level

Analysis set	Level	Statistic	2x daily	4x daily	Total
FAS	1	events/N (%)	5/72 (6.9%)	7/75 (9.3%)	12/147 (8.2%)
		exact 95% CI	[2.29%, 15.47%]	[3.84%, 18.29%]	[4.29%, 13.83%]
	2	events/N (%)	7/72 (9.7%)	6/78 (7.7%)	13/150 (8.7%)
		exact 95% CI	[4.00%, 19.01%]	[2.88%, 15.99%]	[4.70%, 14.36%]
	3	events/N (%)	2/53 (3.8%)	2/62 (3.2%)	4/115 (3.5%)
		exact 95% CI	[0.46%, 12.98%]	[0.39%, 11.17%]	[0.96%, 8.67%]
	Total	events/N (%)	14/197 (7.1%)	15/215 (7.0%)	29/412 (7.0%)
		exact 95% CI	[3.94%, 11.64%]	[3.96%, 11.25%]	[4.76%, 9.95%]
PP	1	events/N (%)	1/62 (1.6%)	2/66 (3.0%)	3/128 (2.3%)
		exact 95% CI	[0.04%, 8.66%]	[0.37%, 10.52%]	[0.49%, 6.70%]
	2	events/N (%)	2/64 (3.1%)	5/73 (6.8%)	7/137 (5.1%)
		exact 95% CI	[0.38%, 10.84%]	[2.26%, 15.26%]	[2.08%, 10.24%]
	3	events/N (%)	0/47 (0.0%)	0/52 (0.0%)	0/99 (0.0%)
		exact 95% CI	[0.00%, 7.55%]	[0.00%, 6.85%]	[0.00%, 3.66%]
	Total	events/N (%)	3/173 (1.7%)	7/191 (3.7%)	10/364 (2.7%)
		exact 95% CI	[0.36%, 4.98%]	[1.49%, 7.41%]	[1.33%, 4.99%]
PP *	1	events/N (%)	1/45 (2.2%)	1/47 (2.1%)	2/92 (2.2%)
		exact 95% CI	[0.06%, 11.77%]	[0.05%, 11.29%]	[0.26%, 7.63%]
	2	events/N (%)	2/64 (3.1%)	5/73 (6.8%)	7/137 (5.1%)
		exact 95% CI	[0.38%, 10.84%]	[2.26%, 15.26%]	[2.08%, 10.24%]
	3	events/N (%)	0/47 (0.0%)	0/52 (0.0%)	0/99 (0.0%)
		exact 95% CI	[0.00%, 7.55%]	[0.00%, 6.85%]	[0.00%, 3.66%]
	Total	events/N (%)	3/156 (1.9%)	6/172 (3.5%)	9/328 (2.7%)
		exact 95% CI	[0.40%, 5.52%]	[1.29%, 7.44%]	[1.26%, 5.14%]

PP *: PP set in the strong sense, created by: t_report.sas

Table 12-85: Treatment failures (day 14) with two-sided 95% CI by group and level

Analysis set	Level	Statistic	2x daily	4x daily	Total
FAS	1	events/N (%)	15/72 (20.8%)	13/75 (17.3%)	28/147 (19.0%)
		exact 95% CI	[12.16%, 32.02%]	[9.57%, 27.81%]	[13.05%, 26.34%]
	2	events/N (%)	13/72 (18.1%)	18/78 (23.1%)	31/150 (20.7%)
		exact 95% CI	[9.98%, 28.89%]	[14.29%, 34.00%]	[14.49%, 28.03%]
	3	events/N (%)	11/53 (20.8%)	14/62 (22.6%)	25/115 (21.7%)
		exact 95% CI	[10.84%, 34.11%]	[12.93%, 34.97%]	[14.59%, 30.40%]
	Total	events/N (%)	39/197 (19.8%)	45/215 (20.9%)	84/412 (20.4%)
		exact 95% CI	[14.47%, 26.05%]	[15.70%, 26.99%]	[16.60%, 24.61%]
PP	1	events/N (%)	6/62 (9.7%)	4/66 (6.1%)	10/128 (7.8%)
		exact 95% CI	[3.63%, 19.88%]	[1.68%, 14.80%]	[3.81%, 13.90%]
	2	events/N (%)	5/64 (7.8%)	13/73 (17.8%)	18/137 (13.1%)
		exact 95% CI	[2.59%, 17.30%]	[9.84%, 28.53%]	[7.98%, 19.97%]
	3	events/N (%)	5/47 (10.6%)	5/52 (9.6%)	10/99 (10.1%)
		exact 95% CI	[3.55%, 23.10%]	[3.20%, 21.03%]	[4.95%, 17.79%]
	Total	events/N (%)	16/173 (9.2%)	22/191 (11.5%)	38/364 (10.4%)
		exact 95% CI	[5.38%, 14.58%]	[7.36%, 16.92%]	[7.49%, 14.05%]
PP *	1	events/N (%)	4/45 (8.9%)	3/47 (6.4%)	7/92 (7.6%)
		exact 95% CI	[2.48%, 21.22%]	[1.34%, 17.54%]	[3.11%, 15.05%]
	2	events/N (%)	5/64 (7.8%)	13/73 (17.8%)	18/137 (13.1%)
		exact 95% CI	[2.59%, 17.30%]	[9.84%, 28.53%]	[7.98%, 19.97%]
	3	events/N (%)	5/47 (10.6%)	5/52 (9.6%)	10/99 (10.1%)
		exact 95% CI	[3.55%, 23.10%]	[3.20%, 21.03%]	[4.95%, 17.79%]
	Total	events/N (%)	14/156 (9.0%)	21/172 (12.2%)	35/328 (10.7%)
		exact 95% CI	[4.99%, 14.60%]	[7.72%, 18.06%]	[7.55%, 14.53%]

PP *: PP set in the strong sense, created by: t_report.sas

Table 12-86: Clinical or parasitological failures (day 14) with 95% CI by group and level

Analysis set	Level	Statistic	2x daily	4x daily	Total
FAS	1	events/N (%)	29/72 (40.3%)	25/75 (33.3%)	54/147 (36.7%)
		exact 95% CI	[28.88%, 52.50%]	[22.86%, 45.17%]	[28.94%, 45.07%]
	2	events/N (%)	36/72 (50.0%)	31/78 (39.7%)	67/150 (44.7%)
		exact 95% CI	[37.98%, 62.02%]	[28.83%, 51.46%]	[36.55%, 52.99%]
	3	events/N (%)	21/53 (39.6%)	24/62 (38.7%)	45/115 (39.1%)
		exact 95% CI	[26.45%, 54.00%]	[26.60%, 51.93%]	[30.16%, 48.67%]
	Total	events/N (%)	86/197 (43.7%)	80/215 (37.2%)	166/412 (40.3%)
		exact 95% CI	[36.62%, 50.89%]	[30.73%, 44.04%]	[35.52%, 45.20%]
PP	1	events/N (%)	21/62 (33.9%)	19/66 (28.8%)	40/128 (31.3%)
		exact 95% CI	[22.33%, 47.01%]	[18.30%, 41.25%]	[23.35%, 40.04%]
	2	events/N (%)	28/64 (43.8%)	26/73 (35.6%)	54/137 (39.4%)
		exact 95% CI	[31.37%, 56.72%]	[24.75%, 47.69%]	[31.18%, 48.12%]
	3	events/N (%)	15/47 (31.9%)	15/52 (28.8%)	30/99 (30.3%)
		exact 95% CI	[19.09%, 47.12%]	[17.13%, 43.08%]	[21.47%, 40.35%]
	Total	events/N (%)	64/173 (37.0%)	60/191 (31.4%)	124/364 (34.1%)
		exact 95% CI	[29.79%, 44.65%]	[24.90%, 38.51%]	[29.21%, 39.19%]
PP *	1	events/N (%)	15/45 (33.3%)	15/47 (31.9%)	30/92 (32.6%)
		exact 95% CI	[20.00%, 48.95%]	[19.09%, 47.12%]	[23.20%, 43.18%]
	2	events/N (%)	28/64 (43.8%)	26/73 (35.6%)	54/137 (39.4%)
		exact 95% CI	[31.37%, 56.72%]	[24.75%, 47.69%]	[31.18%, 48.12%]
	3	events/N (%)	15/47 (31.9%)	15/52 (28.8%)	30/99 (30.3%)
		exact 95% CI	[19.09%, 47.12%]	[17.13%, 43.08%]	[21.47%, 40.35%]
	Total	events/N (%)	58/156 (37.2%)	56/172 (32.6%)	114/328 (34.8%)
		exact 95% CI	[29.59%, 45.27%]	[25.62%, 40.11%]	[29.61%, 40.18%]

PP *: PP set in the strong sense, two-sided 95% confidence intervals, created by: t_report.sas

Table 12-87: Treatment failures (day 28) with 95% CI by group for level 3

Analysis set	Level	Statistic	2x daily	4x daily	Total
FAS	3	events/N (%)	12/53 (22.6%)	20/62 (32.3%)	32/115 (27.8%)
		exact 95% CI	[12.28%, 36.21%]	[20.94%, 45.34%]	[19.87%, 36.95%]
PP	3	events/N (%)	6/47 (12.8%)	10/52 (19.2%)	16/99 (16.2%)
		exact 95% CI	[4.83%, 25.74%]	[9.63%, 32.53%]	[9.53%, 24.91%]
PP *	3	events/N (%)	6/47 (12.8%)	10/52 (19.2%)	16/99 (16.2%)
		exact 95% CI	[4.83%, 25.74%]	[9.63%, 32.53%]	[9.53%, 24.91%]

PP *: PP set in the strong sense, two-sided 95% confidence intervals, created by: t_report.sas

Table 12-88: Clinical or parasitological failures (day 28) with 95% CI by group for level 3

Analysis set	Level	Statistic	2x daily	4x daily	Total
FAS	3	events/N (%)	33/53 (62.3%)	43/62 (69.4%)	76/115 (66.1%)
		exact 95% CI	[47.89%, 75.21%]	[56.35%, 80.44%]	[56.67%, 74.65%]
PP	3	events/N (%)	27/47 (57.4%)	33/52 (63.5%)	60/99 (60.6%)
		exact 95% CI	[42.18%, 71.74%]	[48.96%, 76.38%]	[50.28%, 70.28%]
PP *	3	events/N (%)	27/47 (57.4%)	33/52 (63.5%)	60/99 (60.6%)
		exact 95% CI	[42.18%, 71.74%]	[48.96%, 76.38%]	[50.28%, 70.28%]

PP *: PP set in the strong sense, two-sided 95% confidence intervals, created by: t_report.sas

Table 12-89: Fever clearance time by group and level (FAS)

	2x daily	4x daily	Comparison
Level 1			
- N	72	75	
- Median [CI]	6.0 [5.5; 10.5]	5.8 [5.3; 6.6]	
- Min, Max	0.0, 28.6	0.1, 47.4	
- p-value (Log-Rank)			0.9880
- p-value (Wilcoxon)			0.5422
- p-value (-2Log(LR))			0.9598
Level 2			
- N	72	77	
- Median [CI]	5.3 [4.1; 5.9]	5.4 [2.2; 6.2]	
- Min, Max	0.0, 35.4	0.1, 37.6	
- p-value (Log-Rank)			0.9423
- p-value (Wilcoxon)			0.6975
- p-value (-2Log(LR))			0.8368
Level 3			
- N	53	62	
- Median [CI]	4.4 [1.6; 6.0]	1.9 [1.4; 5.7]	
- Min, Max	0.0, 19.6	0.0, 17.4	
- p-value (Log-Rank)			0.4508
- p-value (Wilcoxon)			0.3522
- p-value (-2Log(LR))			0.5210
All levels			
- N	197	214	
- Median [CI]	5.6 [5.3; 5.9]	5.6 [5.1; 5.9]	
- Min, Max	0.0, 35.4	0.0, 47.4	
- p-value (Log-Rank)			0.7360
- p-value (Wilcoxon)			0.3336
- p-value (-2Log(LR))			0.6174

The median is based on survival techniques. LR=Likelihood Ratio Test. CI=95% confidence interval

Table 12-90: Fever clearance time by group and level (PP)

	2x daily	4x daily	Comparison
Level 1			
- N	45	47	
- Median [CI]	5.8 [5.4; 10.4]	5.6 [4.9; 6.8]	
- Min, Max	0.0, 28.6	0.1, 36.8	
- p-value (Log-Rank)			0.6742
- p-value (Wilcoxon)			0.7910
- p-value (-2Log(LR))			0.7911
Level 2			
- N	64	73	
- Median [CI]	5.3 [4.1; 5.8]	5.3 [1.5; 6.2]	
- Min, Max	0.0, 35.4	0.1, 37.6	
- p-value (Log-Rank)			0.9497
- p-value (Wilcoxon)			0.6748
- p-value (-2Log(LR))			0.8562
Level 3			
- N	47	52	
- Median [CI]	1.9 [1.5; 5.7]	1.6 [1.2; 5.7]	
- Min, Max	0.0, 19.4	0.0, 17.4	
- p-value (Log-Rank)			0.8292
- p-value (Wilcoxon)			0.5134
- p-value (-2Log(LR))			0.8404
All levels			
- N	156	172	
- Median [CI]	5.4 [4.6; 5.8]	5.4 [4.4; 5.8]	
- Min, Max	0.0, 35.4	0.0, 37.6	
- p-value (Log-Rank)			0.8054
- p-value (Wilcoxon)			0.5734
- p-value (-2Log(LR))			0.9565

The median is based on survival techniques. LR=Likelihood Ratio Test. CI=95% confidence interval

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Table 12-91: Parasite clearance time by group and level (FAS)

	2x daily	4x daily	Comparison
Level 1			
- N	72	73	
- Median [CI]	67.6 [66.6; 68.4]	68.1 [67.7; 68.4]	
- Min, Max	20.5, 95.0	18.8, 92.9	
- p-value (Log-Rank)			0.5022
- p-value (Wilcoxon)			0.5937
- p-value (-2Log(LR))			0.9912
Level 2			
- N	71	77	
- Median [CI]	68.1 [67.7; 69.0]	67.8 [67.3; 68.7]	
- Min, Max	19.9, 93.9	42.9, 94.9	
- p-value (Log-Rank)			0.7201
- p-value (Wilcoxon)			0.3870
- p-value (-2Log(LR))			0.7067
Level 3			
- N	53	62	
- Median [CI]	69.0 [68.3; 69.4]	68.1 [67.5; 68.7]	
- Min, Max	21.5, 94.0	19.4, 94.2	
- p-value (Log-Rank)			0.3392
- p-value (Wilcoxon)			0.0835
- p-value (-2Log(LR))			0.7574
All levels			
- N	196	212	
- Median [CI]	68.3 [67.8; 68.8]	68.0 [67.7; 68.3]	
- Min, Max	19.9, 95.0	18.8, 94.9	
- p-value (Log-Rank)			0.3196
- p-value (Wilcoxon)			0.2928
- p-value (-2Log(LR))			0.6962

The median is based on survival techniques. LR=Likelihood Ratio Test. CI=95% confidence interval

Table 12-92: Parasite clearance time by group and level (PP)

	2x daily	4x daily	Comparison
Level 1			
- N	62	66	
- Min, Max	42.5, 95.0	18.8, 92.9	
- Median [CI]	67.5 [66.6; 68.3]	68.0 [67.0; 68.4]	
- p-value (Log-Rank)			0.2990
- p-value (Wilcoxon)			0.7093
- p-value (-2Log(LR))			0.8430
Level 2			
- N	64	73	
- Min, Max	42.1, 93.9	42.9, 94.9	
- Median [CI]	68.2 [67.7; 69.0]	67.8 [67.3; 68.7]	
- p-value (Log-Rank)			0.7559
- p-value (Wilcoxon)			0.4233
- p-value (-2Log(LR))			0.8107
Level 3			
- N	47	52	
- Min, Max	44.0, 94.0	43.6, 94.2	
- Median [CI]	69.0 [68.4; 69.4]	68.1 [67.5; 68.9]	
- p-value (Log-Rank)			0.4679
- p-value (Wilcoxon)			0.1228
- p-value (-2Log(LR))			0.7736
All levels			
- N	173	191	
- Min, Max	42.1, 95.0	18.8, 94.9	
- Median [CI]	68.3 [67.8; 68.8]	68.0 [67.6; 68.3]	
- p-value (Log-Rank)			0.2735
- p-value (Wilcoxon)			0.2698
- p-value (-2Log(LR))			0.6864

The median is based on survival techniques. LR=Likelihood Ratio Test. CI=95% confidence interval

Table 12-93: Parasite clearance time by group and level (PP in the strong sense)

	2x daily	4x daily	Comparison
Level 1			
- N	45	47	
- Median [CI]	67.0 [66.2; 68.3]	68.0 [67.0; 68.6]	
- Min, Max	42.5, 94.5	18.8, 92.9	
- p-value (Log-Rank)			0.5432
- p-value (Wilcoxon)			0.4979
- p-value (-2Log(LR))			0.8904
Level 2			
- N	64	73	
- Median [CI]	68.2 [67.7; 69.0]	67.8 [67.3; 68.7]	
- Min, Max	42.1, 93.9	42.9, 94.9	
- p-value (Log-Rank)			0.7416
- p-value (Wilcoxon)			0.3928
- p-value (-2Log(LR))			0.7901
Level 3			
- N	47	52	
- Median [CI]	69.0 [68.4; 69.4]	68.1 [67.5; 68.9]	
- Min, Max	44.0, 94.0	43.6, 94.2	
- p-value (Log-Rank)			0.4679
- p-value (Wilcoxon)			0.1228
- p-value (-2Log(LR))			0.7736
All levels			
- N	156	172	
- Median [CI]	68.3 [67.8; 68.9]	68.0 [67.6; 68.4]	
- Min, Max	42.1, 94.5	18.8, 94.9	
- p-value (Log-Rank)			0.4661
- p-value (Wilcoxon)			0.2939
- p-value (-2Log(LR))			0.6953

The median is based on survival techniques. LR=Likelihood Ratio Test. CI=95% confidence interval

Table 12-94: AE overview by group and level (FAS)

Dose level	txt	2x daily	4x daily	Total
1	Num. of Pat. with >=1 AE	25/72 (34.7%)	23/75 (30.7%)	48/147 (32.7%)
	Num. of AEs	30	27	57
2	Num. of Pat. with >=1 AE	9/72 (12.5%)	12/78 (15.4%)	21/150 (14.0%)
	Num. of AEs	9	12	21
3	Num. of Pat. with >=1 AE	5/53 (9.4%)	10/62 (16.1%)	15/115 (13.0%)
	Num. of AEs	7	11	18
Total	Num. of Pat. with >=1 AE	39/197 (19.8%)	45/215 (20.9%)	84/412 (20.4%)
	Num. of AEs	46	50	96
1	Num. of Pat. with >=1 RAE	./72 (. %)	./75 (. %)	./147 (. %)
	Num. of RAEs	.	.	.
2	Num. of Pat. with >=1 RAE	1/72 (1.4%)	1/78 (1.3%)	2/150 (1.3%)
	Num. of RAEs	1	1	2
3	Num. of Pat. with >=1 RAE	./53 (. %)	1/62 (1.6%)	1/115 (0.9%)
	Num. of RAEs	.	1	1
Total	Num. of Pat. with >=1 RAE	1/197 (0.5%)	2/215 (0.9%)	3/412 (0.7%)
	Num. of RAEs	1	2	3
1	Num. of Pat. with >=1 SAE	./72 (. %)	./75 (. %)	./147 (. %)
	Num. of SAEs	.	.	.
2	Num. of Pat. with >=1 SAE	1/72 (1.4%)	1/78 (1.3%)	2/150 (1.3%)
	Num. of SAEs	1	1	2
3	Num. of Pat. with >=1 SAE	./53 (. %)	1/62 (1.6%)	1/115 (0.9%)
	Num. of SAEs	.	1	1
Total	Num. of Pat. with >=1 SAE	1/197 (0.5%)	2/215 (0.9%)	3/412 (0.7%)
	Num. of SAEs	1	2	3
1	Num. of Pat. with >=1 non-SAE	25/72 (34.7%)	23/75 (30.7%)	48/147 (32.7%)
	Num. of non-SAEs	30	27	57
2	Num. of Pat. with >=1 non-SAE	8/72 (11.1%)	11/78 (14.1%)	19/150 (12.7%)
	Num. of non-SAEs	8	11	19
3	Num. of Pat. with >=1 non-SAE	5/53 (9.4%)	10/62 (16.1%)	15/115 (13.0%)
	Num. of non-SAEs	7	10	17
Total	Num. of Pat. with >=1 non-SAE	38/197 (19.3%)	44/215 (20.5%)	82/412 (19.9%)
	Num. of non-SAEs	45	48	93

created by t_report.sas

Table 12-95: Number of SAEs with two-sided CI by analysis population, group, and level

Analysis set	level	statistic	2x daily	4x daily	Total
FAS	1	events/N (%)	0/72 (0.0%)	0/75 (0.0%)	0/147 (0.0%)
		exact 95% CI	[0.00%, 4.99%]	0.00%, 4.80%]	0.00%, 2.48%]
	2	events/N (%)	1/72 (1.4%)	1/78 (1.3%)	2/150 (1.3%)
		exact 95% CI	[0.04%, 7.50%]	0.03%, 6.94%]	0.16%, 4.73%]
	3	events/N (%)	0/53 (0.0%)	1/62 (1.6%)	1/115 (0.9%)
		exact 95% CI	[0.00%, 6.72%]	0.04%, 8.66%]	0.02%, 4.75%]
	Total	events/N (%)	1/197 (0.5%)	2/215 (0.9%)	3/412 (0.7%)
		exact 95% CI	[0.01%, 2.80%]	0.11%, 3.32%]	0.15%, 2.11%]
PP	1	events/N (%)	0/62 (0.0%)	0/66 (0.0%)	0/128 (0.0%)
		exact 95% CI	[0.00%, 5.78%]	0.00%,5.44%]	0.00%, 2.84%]
	2	events/N (%)	0/64 (0.0%)	0/73 (0.0%)	0/137 (0.0%)
		exact 95% CI	[0.00%, 5.60%]	0.00%,4.93%]	0.00%, 2.66%]
	3	events/N (%)	0/47 (0.0%)	1/52 (1.9%)	1/99 (1.0%)
		exact 95% CI	[0.00%, 7.55%]	0.05%,10.26%]	0.03%, 5.50%]
	Total	events/N (%)	0/173 (0.0%)	1/191 (0.5%)	1/364 (0.3%)
		exact 95% CI	[0.00%, 2.11%]	0.01%, 2.88%]	0.01%,1.52%]
PP *	1	events/N (%)	0/45 (0.0%)	0/47 (0.0%)	0/92 (0.0%)
		exact 95% CI	[0.00%, 7.87%]	0.00%, 7.55%]	0.00%, 3.93%]
	2	events/N (%)	0/64 (0.0%)	0/73 (0.0%)	0/137 (0.0%)
		exact 95% CI	[0.00%, 5.60%]	0.00%, 4.93%]	0.00%, 2.66%]
	3	events/N (%)	0/47 (0.0%)	1/52 (1.9%)	1/99 (1.0%)
		exact 95% CI	[0.00%, 7.55%]	0.05%,10.26%]	0.03%, 5.50%]
	Total	events/N (%)	0/156 (0.0%)	1/172 (0.6%)	1/328 (0.3%)
		exact 95% CI	[0.00%, 2.34%]	0.01%,3.20%]	0.01%, 1.69%]

* PP in the strong sense; if 0 events occured the CI is automatically one-sided

Table 12-96: Adverse events by PT Term for Level 1 (FAS)

	2x daily (N=72)	4x daily (N=75)	Total (N=147)
Number of AE's (=100%)	30(100.0%)	27(100.0%)	57(100.0%)
PT Term			
- Bronchitis acute	11(36.7%)	6(22.2%)	17(29.8%)
- Diarrhoea	6(20.0%)	7(25.9%)	13(22.8%)
- Vomiting	5(16.7%)	2(7.4%)	7(12.3%)
- Dysentery	3(10.0%)	3(11.1%)	6(10.5%)
- Pruritus	2(6.7%)	1(3.7%)	3(5.3%)
- Skin infection	0(0.0%)	3(11.1%)	3(5.3%)
- Nasopharyngitis	1(3.3%)	1(3.7%)	2(3.5%)
- Abdominal pain	0(0.0%)	1(3.7%)	1(1.8%)
- Cough	0(0.0%)	1(3.7%)	1(1.8%)
- Dysuria	1(3.3%)	0(0.0%)	1(1.8%)
- Folliculitis	0(0.0%)	1(3.7%)	1(1.8%)
- Nausea	1(3.3%)	0(0.0%)	1(1.8%)
- Strongyloidiasis	0(0.0%)	1(3.7%)	1(1.8%)

percentages are based on the number of AE's by group

Table 12-97: Adverse events by PT Term for Level 2 (FAS)

	2x daily (N=72)	4x daily (N=78)	Total (N=150)
Number of AE's (=100%)	9(100.0%)	12(100.0%)	21(100.0%)
PT Term			
- Pruritus	1(11.1%)	3(25.0%)	4(19.0%)
- Bronchitis acute	1(11.1%)	2(16.7%)	3(14.3%)
- Diarrhoea	0(0.0%)	3(25.0%)	3(14.3%)
- Vomiting	2(22.2%)	1(8.3%)	3(14.3%)
- Aphthous stomatitis	0(0.0%)	1(8.3%)	1(4.8%)
- Cerebral malaria	1(11.1%)	0(0.0%)	1(4.8%)
- Dysuria	1(11.1%)	0(0.0%)	1(4.8%)
- Gastroenteritis	0(0.0%)	1(8.3%)	1(4.8%)
- Hookworm infection	1(11.1%)	0(0.0%)	1(4.8%)
- Nasopharyngitis	1(11.1%)	0(0.0%)	1(4.8%)
- Otitis media acute	1(11.1%)	0(0.0%)	1(4.8%)
- Trichomoniasis intestinal	0(0.0%)	1(8.3%)	1(4.8%)

percentages are based on the number of AE's by group

Table 12-98: Adverse events by PT Term for Level 3 (FAS)

	2x daily (N=53)	4x daily (N=62)	Total (N=115)
Number of AE's (=100%)	7(100.0%)	11(100.0%)	18(100.0%)
PT Term			
- Dysentery	1(14.3%)	2(18.2%)	3(16.7%)
- Pruritus	1(14.3%)	2(18.2%)	3(16.7%)
- Diarrhoea	0(0.0%)	2(18.2%)	2(11.1%)
- Nasopharyngitis	2(28.6%)	0(0.0%)	2(11.1%)
- Anaemia	0(0.0%)	1(9.1%)	1(5.6%)
- Bronchitis acute	0(0.0%)	1(9.1%)	1(5.6%)
- Cough	0(0.0%)	1(9.1%)	1(5.6%)
- Dyspnoea	0(0.0%)	1(9.1%)	1(5.6%)
- Dysuria	1(14.3%)	0(0.0%)	1(5.6%)
- Rhinitis	0(0.0%)	1(9.1%)	1(5.6%)
- Strongyloidiasis	1(14.3%)	0(0.0%)	1(5.6%)
- Trichomoniasis intestinal	1(14.3%)	0(0.0%)	1(5.6%)

percentages are based on the number of AE's by group

Table 12-99: Adverse events by PT Term for all Levels (FAS)

	2x daily (N=197)	4x daily (N=215)	Total (N=412)
Number of AE's (=100%)	46(100.0%)	50(100.0%)	96(100.0%)
PT Term			
- Bronchitis acute	12(26.1%)	9(18.0%)	21(21.9%)
- Diarrhoea	6(13.0%)	12(24.0%)	18(18.8%)
- Pruritus	4(8.7%)	6(12.0%)	10(10.4%)
- Vomiting	7(15.2%)	3(6.0%)	10(10.4%)
- Dysentery	4(8.7%)	5(10.0%)	9(9.4%)
- Nasopharyngitis	4(8.7%)	1(2.0%)	5(5.2%)
- Dysuria	3(6.5%)	0(0.0%)	3(3.1%)
- Skin infection	0(0.0%)	3(6.0%)	3(3.1%)
- Cough	0(0.0%)	2(4.0%)	2(2.1%)
- Strongyloidiasis	1(2.2%)	1(2.0%)	2(2.1%)
- Trichomoniasis intestinal	1(2.2%)	1(2.0%)	2(2.1%)
- Abdominal pain	0(0.0%)	1(2.0%)	1(1.0%)
- Anaemia	0(0.0%)	1(2.0%)	1(1.0%)
- Aphthous stomatitis	0(0.0%)	1(2.0%)	1(1.0%)
- Cerebral malaria	1(2.2%)	0(0.0%)	1(1.0%)
- Dyspnoea	0(0.0%)	1(2.0%)	1(1.0%)
- Folliculitis	0(0.0%)	1(2.0%)	1(1.0%)
- Gastroenteritis	0(0.0%)	1(2.0%)	1(1.0%)
- Hookworm infection	1(2.2%)	0(0.0%)	1(1.0%)
- Nausea	1(2.2%)	0(0.0%)	1(1.0%)
- Otitis media acute	1(2.2%)	0(0.0%)	1(1.0%)
- Rhinitis	0(0.0%)	1(2.0%)	1(1.0%)

percentages are based on the number of AE's by group

Table 12-100: Adverse events by HLT Term for Level 1 (FAS)

	2x daily (N=72)	4x daily (N=75)	Total (N=147)
Number of AE's (=100%)	30(100.0%)	27(100.0%)	57(100.0%)
HLT Term			
- Lower respiratory tract and lung infections	11(36.7%)	6(22.2%)	17(29.8%)
- Diarrhoea (excl infective)	6(20.0%)	7(25.9%)	13(22.8%)
- Nausea and vomiting symptoms	6(20.0%)	2(7.4%)	8(14.0%)
- Abdominal and gastrointestinal infections	3(10.0%)	3(11.1%)	6(10.5%)
- Pruritus NEC	2(6.7%)	1(3.7%)	3(5.3%)
- Skin structures and soft tissue infections	0(0.0%)	3(11.1%)	3(5.3%)
- Upper respiratory tract infections	1(3.3%)	1(3.7%)	2(3.5%)
- Bacterial infections NEC	0(0.0%)	1(3.7%)	1(1.8%)
- Bladder and urethral symptoms	1(3.3%)	0(0.0%)	1(1.8%)
- Coughing and associated symptoms	0(0.0%)	1(3.7%)	1(1.8%)
- Gastrointestinal and abdominal pains (excl oral and throat)	0(0.0%)	1(3.7%)	1(1.8%)
- Nematode infections	0(0.0%)	1(3.7%)	1(1.8%)

percentages are based on the number of AE's by group

Table 12-101: Adverse events by HLT Term for Level 2 (FAS)

	2x daily (N=72)	4x daily (N=78)	Total (N=150)
Number of AE's (=100%)	9(100.0%)	12(100.0%)	21(100.0%)
HLT Term			
- Pruritus NEC	1(11.1%)	3(25.0%)	4(19.0%)
- Diarrhoea (excl infective)	0(0.0%)	3(25.0%)	3(14.3%)
- Lower respiratory tract and lung infections	1(11.1%)	2(16.7%)	3(14.3%)
- Nausea and vomiting symptoms	2(22.2%)	1(8.3%)	3(14.3%)
- Abdominal and gastrointestinal infections	0(0.0%)	1(8.3%)	1(4.8%)
- Bladder and urethral symptoms	1(11.1%)	0(0.0%)	1(4.8%)
- Ear infections	1(11.1%)	0(0.0%)	1(4.8%)
- Encephalitis nonviral infectious	1(11.1%)	0(0.0%)	1(4.8%)
- Nematode infections	1(11.1%)	0(0.0%)	1(4.8%)
- Protozoal infections NEC	0(0.0%)	1(8.3%)	1(4.8%)
- Stomatitis and ulceration	0(0.0%)	1(8.3%)	1(4.8%)
- Upper respiratory tract infections	1(11.1%)	0(0.0%)	1(4.8%)

percentages are based on the number of AE's by group

Table 12-102: Adverse events by HLT Term for Level 3 (FAS)

	2x daily (N=53)	4x daily (N=62)	Total (N=115)
Number of AE's (=100%)	7(100.0%)	11(100.0%)	18(100.0%)
HLT Term			
- Abdominal and gastrointestinal infections	1(14.3%)	2(18.2%)	3(16.7%)
- Pruritus NEC	1(14.3%)	2(18.2%)	3(16.7%)
- Upper respiratory tract infections	2(28.6%)	1(9.1%)	3(16.7%)
- Diarrhoea (excl infective)	0(0.0%)	2(18.2%)	2(11.1%)
- Anaemias NEC	0(0.0%)	1(9.1%)	1(5.6%)
- Bladder and urethral symptoms	1(14.3%)	0(0.0%)	1(5.6%)
- Breathing abnormalities	0(0.0%)	1(9.1%)	1(5.6%)
- Coughing and associated symptoms	0(0.0%)	1(9.1%)	1(5.6%)
- Lower respiratory tract and lung infections	0(0.0%)	1(9.1%)	1(5.6%)
- Nematode infections	1(14.3%)	0(0.0%)	1(5.6%)
- Protozoal infections NEC	1(14.3%)	0(0.0%)	1(5.6%)

percentages are based on the number of AE's by group

Table 12-103: Adverse events by HLT Term for all Levels (FAS)

	2x daily (N=197)	4x daily (N=215)	Total (N=412)
Number of AE's (=100%)	46(100.0%)	50(100.0%)	96(100.0%)
HLT Term			
- Lower respiratory tract and lung infections	12(26.1%)	9(18.0%)	21(21.9%)
- Diarrhoea (excl infective)	6(13.0%)	12(24.0%)	18(18.8%)
- Nausea and vomiting symptoms	8(17.4%)	3(6.0%)	11(11.5%)
- Abdominal and gastrointestinal infections	4(8.7%)	6(12.0%)	10(10.4%)
- Pruritus NEC	4(8.7%)	6(12.0%)	10(10.4%)
- Upper respiratory tract infections	4(8.7%)	2(4.0%)	6(6.3%)
- Bladder and urethral symptoms	3(6.5%)	0(0.0%)	3(3.1%)
- Nematode infections	2(4.3%)	1(2.0%)	3(3.1%)
- Skin structures and soft tissue infections	0(0.0%)	3(6.0%)	3(3.1%)
- Coughing and associated symptoms	0(0.0%)	2(4.0%)	2(2.1%)
- Protozoal infections NEC	1(2.2%)	1(2.0%)	2(2.1%)
- Anaemias NEC	0(0.0%)	1(2.0%)	1(1.0%)
- Bacterial infections NEC	0(0.0%)	1(2.0%)	1(1.0%)
- Breathing abnormalities	0(0.0%)	1(2.0%)	1(1.0%)
- Ear infections	1(2.2%)	0(0.0%)	1(1.0%)
- Encephalitis nonviral infectious	1(2.2%)	0(0.0%)	1(1.0%)
- Gastrointestinal and abdominal pains (excl oral and throat)	0(0.0%)	1(2.0%)	1(1.0%)
- Stomatitis and ulceration	0(0.0%)	1(2.0%)	1(1.0%)

percentages are based on the number of AE's by group

Table 12-104: Adverse events by HLGT Term for Level 1 (FAS)

	2x daily (N=72)	4x daily (N=75)	Total (N=147)
Number of AE's (=100%)	30(100.0%)	27(100.0%)	57(100.0%)
HLGT Term			
- Infections - pathogen class unspecified	15(50.0%)	13(48.1%)	28(49.1%)
- Gastrointestinal motility and defaecation conditions	6(20.0%)	7(25.9%)	13(22.8%)
- Gastrointestinal signs and symptoms	6(20.0%)	3(11.1%)	9(15.8%)
- Epidermal and dermal conditions	2(6.7%)	1(3.7%)	3(5.3%)
- Bacterial infectious disorders	0(0.0%)	1(3.7%)	1(1.8%)
- Helminthic disorders	0(0.0%)	1(3.7%)	1(1.8%)
- Respiratory disorders NEC	0(0.0%)	1(3.7%)	1(1.8%)
- Urinary tract signs and symptoms	1(3.3%)	0(0.0%)	1(1.8%)

percentages are based on the number of AE's by group

Table 12-105: Adverse events by HLGT Term for Level 2 (FAS)

	2x daily (N=72)	4x daily (N=78)	Total (N=150)
Number of AE's (=100%)	9(100.0%)	12(100.0%)	21(100.0%)
HLGT Term			
- Infections - pathogen class unspecified	3(33.3%)	3(25.0%)	6(28.6%)
- Epidermal and dermal conditions	1(11.1%)	3(25.0%)	4(19.0%)
- Gastrointestinal motility and defaecation conditions	0(0.0%)	3(25.0%)	3(14.3%)
- Gastrointestinal signs and symptoms	2(22.2%)	1(8.3%)	3(14.3%)
- Central nervous system infections and inflammations	1(11.1%)	0(0.0%)	1(4.8%)
- Helminthic disorders	1(11.1%)	0(0.0%)	1(4.8%)
- Oral soft tissue conditions	0(0.0%)	1(8.3%)	1(4.8%)
- Protozoal infectious disorders	0(0.0%)	1(8.3%)	1(4.8%)
- Urinary tract signs and symptoms	1(11.1%)	0(0.0%)	1(4.8%)

percentages are based on the number of AE's by group

Table 12-106: Adverse events by HLGT Term for Level 3 (FAS)

	2x daily (N=53)	4x daily (N=62)	Total (N=115)
Number of AE's (=100%)	7(100.0%)	11(100.0%)	18(100.0%)
HLGT Term			
- Infections - pathogen class unspecified	3(42.9%)	4(36.4%)	7(38.9%)
- Epidermal and dermal conditions	1(14.3%)	2(18.2%)	3(16.7%)
- Gastrointestinal motility and defaecation conditions	0(0.0%)	2(18.2%)	2(11.1%)
- Respiratory disorders NEC	0(0.0%)	2(18.2%)	2(11.1%)
- Anaemias nonhaemolytic and marrow depression	0(0.0%)	1(9.1%)	1(5.6%)
- Helminthic disorders	1(14.3%)	0(0.0%)	1(5.6%)
- Protozoal infectious disorders	1(14.3%)	0(0.0%)	1(5.6%)
- Urinary tract signs and symptoms	1(14.3%)	0(0.0%)	1(5.6%)

percentages are based on the number of AE's by group

Table 12-107: Adverse events by HLGT Term for all Levels (FAS)

	2x daily (N=197)	4x daily (N=215)	Total (N=412)
Number of AE's (=100%)	46(100.0%)	50(100.0%)	96(100.0%)
HLGT Term			
- Infections - pathogen class unspecified	21(45.7%)	20(40.0%)	41(42.7%)
- Gastrointestinal motility and defaecation conditions	6(13.0%)	12(24.0%)	18(18.8%)
- Gastrointestinal signs and symptoms	8(17.4%)	4(8.0%)	12(12.5%)
- Epidermal and dermal conditions	4(8.7%)	6(12.0%)	10(10.4%)
- Helminthic disorders	2(4.3%)	1(2.0%)	3(3.1%)
- Respiratory disorders NEC	0(0.0%)	3(6.0%)	3(3.1%)
- Urinary tract signs and symptoms	3(6.5%)	0(0.0%)	3(3.1%)
- Protozoal infectious disorders	1(2.2%)	1(2.0%)	2(2.1%)
- Anaemias nonhaemolytic and marrow depression	0(0.0%)	1(2.0%)	1(1.0%)
- Bacterial infectious disorders	0(0.0%)	1(2.0%)	1(1.0%)
- Central nervous system infections and inflammations	1(2.2%)	0(0.0%)	1(1.0%)
- Oral soft tissue conditions	0(0.0%)	1(2.0%)	1(1.0%)

percentages are based on the number of AE's by group