Artequin™ Paediatric Stickpack

Module 2.7. Clinical Summary

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2.7.1 SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

2.7.1.1 Background and Overview

Malaria is the most important of all tropical diseases and despite considerable efforts to eradicate or control the disease, malaria continues to be a major cause of human morbidity and mortality in the tropics, particularly in Africa and South-East Asia.

Artequin is a fixed-dose combination of artesunate and mefloquine for the treatment of malaria. It is a member of a group of antimalaria drugs called ACT's (artemisinin based combination drugs). The detailed medical background on malaria and ACT's is provided in the Clinical Overview on "Artequin Paediatric Stickpack".

So far, Artequin was only available as co-packed blisters containing artesunate and mefloquine in tablet form. The treatments were only suitable for children able to swallow tablets and with a body weight of more than 20 kg.

The new "Artequin Paediatric Stickpack" formulation presented in this Clinical Summary is a flavoured, taste-masked preparation of granules of 50 mg artesunate and 125 mg mefloquine as a fixed-dose combination (once daily one single Stickpack for 3-days). It is suitable for children with body weight from 10 to 20 kg.

To substantiate the final goal of the clinical development of Artequin, i.e., to complete the dosage range of oral Artequin as a dose-linear line extension of the solid oral forms (tablets) of Artequin 300/750 for children (body weight range of >20 to 40 kg) and Artequin 600/1500 for adults, a series of pharmacokinetic (PK) investigations have been carried out, namely:

Study code	Study title
1) CS 111	Relative bioavailability of a new tablet formulation of MEPHAQUIN LACTABS® from Mepha Ltd. and LARIAM® from Hoffmann-La Roche Ltd. under fed conditions in healthy volunteers.
2) ART-INT-01-2005	An assessment of the pharmacokinetic interaction between artesunate and mefloquine in healthy Caucasian volunteers.
3) SPC 25-16	Randomized, single-dose, 3-way cross-over study to investigate the bioequivalence of two dosage forms of artesunate and to investigate the dose proportionality of artesunate pharmacokinetics (Plasmotrim™ Lactab™ oblong).
4) AM-P 001-2005/ SPC 25-21	Open-label, stratified study on the efficacy, safety and pharmacokinetic characteristics of two paediatric formulations of Artequin™ in children with acute uncomplicated P. falciparum malaria.

Table 1: Studies presented in this section

2.7.1.2 Summary of Results of Individual Studies

2.7.1.2.1 Bioequivalence between Mephaquin® and Lariam®

Study CS 111

In a 2-way cross-over, open-label, single-dose study the relative bioavailability of Mephaquin™ Lactab™, Mepha Ltd (mefloquine), compared with the standard formulation (Lariam® 250 mg, Hoffmann-La Roche Ltd) was investigated (*n* = 40). According to a pre-defined randomization schedule, all subjects received the mefloquine dose, i.e. a single oral dose (3 x 250 mg) of either Mephaquin™ Lactabs™ (Treatment A) or Lariam® (Treatment B).

Blood samples were collected at pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 96, 168, 336, 504, 672, 1008, 1344, 1680 and 2016 hours post dose.

After completion of Period I of the study, subjects entered a 9 week washout period prior to crossing over to Period II. All procedures in Period II were identical to those described for Period I with subjects receiving the alternative treatment.

A standard bioequivalence analysis was conducted based on the two one-sided t-test procedure for log transformed AUC and C_{max} values. 90% confidence intervals were calculated for both parameters and evaluated against regulatory standards of 80 - 125 % (test/reference).

Two subjects did not complete the study for reasons unrelated to the study drug. The results from the remaining 38 subjects are summarized below:

Parameter	Mephaquin®	Lariam®	Ratio	Lower 90 % Conf. Limit	Upper 90 % Conf. Limit
AUC (ng/ml·h)	530 388	522 581	1.015	95.8 %	109.3 %
C_{max} (ng/ml)	1372.9	1314.9	1.044	98.2 %	110.5 %
t_{max} (h)*	6	6	-	-	-
Half-life (h)	440.7	440.2	-	-	-

Table 2: PK-parameters and statistical evaluation
* Median

The 90% confidence interval for both AUC and C_{max} met regulatory standards. The relative bioavailability of Mephaquin™ Lactab™ to Lariam® with food was 101.5 % based on the AUC ratio and for C_{max} the ratio was 104.4 %. The 90% confidence intervals were well within the acceptable range for bioequivalence (80-125%). Thus, Mephaquin™ is bioequivalent to Lariam® for both extent and rate of absorption when administered together with food.

2.7.1.2.2 Pharmacokinetic interaction study with artesunate and mefloquine

ART-INT-01-2005

An open-label, multiple-dose, one-sequence crossover 2-period study with a minimum washout period of 21 days between the two periods was conducted as follows:

At least 16 evaluable subjects were requested per protocol to undergo two 3-day pharmacokinetic periods (A and B) of artesunate, the first with the drug given alone and the second together with mefloquine. The two periods were separated by at least 21 days. 21 subjects completed both arms of the study, 20 were evaluable for PK analysis.
In period A patients were administered one 200 mg tablet of artesunate daily for 3 days and in period B, 200 mg of artesunate together with 250 mg of mefloquine daily for 3 days (therapeutic concept of Artequin 600/750) in a fasted state.
Plasma samples for determination of the pharmacokinetics of Dihydroartemisinin (DHA) and artesunate were obtained over an 8-hour period on day 1 and 3 of each period (0, 0.5, 1, 2, 3, 4, 5, 6, 8 h). In addition, plasma samples for mefloquine were obtained during period B as follows:
- Day 1 and 3: Pre-dose; 4; and 8 hours
- Day 2: Pre-dose, and 4 hours
- Follow up (days 4, 5, and 6): Any time during the follow-up visits

PK-parameters DHA:

	Arithmetic Mean±SD				Median
	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-}\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	t_{max} (h)
Period A, day 1	696±175	1468±463	1503±466	1.14±0.39	0.96±0.83
Period A, day 3	680±222	1382±384	1414±383	1.14±0.37	0.75±0.42
Period B, day 1	546±215	1268±522	1300±524	1.09±0.33	1.02±0.90
Period B, day 3	660±313	1371±609	1402±607	1.09±0.41	0.92±0.47

Table 3: PK-parameters for DHA
Period A: Artesunate alone; Period B: Artesunate plus Mefloquine

PK-parameters artesunate:

According to the protocol, analysis of artesunate plasma concentration time profiles was planned in case that there would be sufficient data points in spite of the short half live of artesunate.
C_{max} and T_{max} were the only parameters examined as there were at best 2-3 data points that had measurable concentrations of artesunate. These data were not sufficient to provide a robust estimate of $T_{1/2}$ or other secondary parameters such as AUC etc.

	Period A, day 1		Period A, day 3		Period B, day 1		Period B, day 3	
	Cmax	Tmax	Cmax	Tmax	Cmax	Tmax	Cmax	Tmax
Mean	189	0.50	173	0.50	122	0.42	165	0.42
SD	159	0.42	178	0.42	129	0.33	137	0.42
95CI	68	0.92	76	0.83	55	0.5	59	0.5425

Table 4: PK-parameters artesunate
Period A: Artesunate alone; Period B: Artesunate plus Mefloquine

PK-parameters mefloquine:

The data set for mefloquine had only a limited sampling schedule. Therefore, the only pharmacokinetic descriptors provided are $AUC_{0\text{-last}}$ and C_{av} (average concentration achieved over the course of the study = $AUC_{0\text{-last}}$ /last study time).

Subject	AUC $_{0\text{-last}}$ (ng.h/mL)	Time$_{last}$ (h)	Cav (ng/mL)
Mean	101885	132.50	769
SD	49371	48.30	270
95CI	21116	20.66	115
95CI lower	80769	111.84	653
95CI upper	123001	113.59	735

Table 5: PK-evaluation mefloquine
AUC0-last: Area under the curve from timepoint 0 (Period B, day1) to time of last mefloquine measurement (=Timelast)
Timelast: Time of last mefloquine measurement
Cav: Average (Cav) concentration over the 0 to last time period was calculated as the AUC0-last./the time

The primary objective of the study was to compare $AUC_{0\text{-inf}}$ for DHA on day 3 of period A as compared to day 3 of period B. The $AUC_{0\text{-inf}}$ of DHA of period A, day 3 was taken as the Reference (R) and that of period B, day 3 as the Test (T), i.e., on the 3rd day of artesunate treatment without and after concomitant mefloquine administration, the mean percentage T/R was 102% (n=20) with a 90% confidence interval of 87-117%. This interval lies within the 80-125% boundaries for bioequivalence specified by the FDA, confirming that there is no significant effect of mefloquine on DHA PK characteristics.

2.7.1.2.3 Bioequivalence and dose proportionality of oral artesunate

Study SPC 25-16

To compare the rate and extent of absorption of artesunate from 50 mg artesunate tablets (Plasmotrim-50) as compared to 200 mg artesunate tablets (Plasmotrim-200), both given in the identical galenical composition as of all artesunate tablets presented in the Co-blister formulation of Artequin, and to investigate the dose proportionality of artesunate, an open-label, randomized, single dose, 3-way crossover study was carried out on 24 healthy male subjects in the fasting state. The minimum washout period between doses was 7 days.

Each subject received three single oral doses of artesunate with identical, i.e., dose-linear galenical composition: one dose of 50 mg (to investigate the linearity of the pharmacokinetics), one dose of 4 x 50 mg (to compare the galenical formulations) and one dose of 200 mg as the reference. Blood for determination of artesunate and dihydroartemisinin (DHA) plasma concentrations were taken at pre-dose, 10min, 20min, 30min, 45min, 1h, 1h15min, 1h30min, 1h45min, 2h, 2h30min, 3h, 4h, 6h, 8h, 12h, 16h and 24h after each administration. Samples were analyzed by a validated LC-MS/MS method.

For statistical evaluation of the relative equivalence of the 4x50 mg versus 1x200 mg artesunate tablets, the narrow 90% acceptance interval of 80% - 125% for DHA AUC and the extended interval of 70%-143% for DHA C_{max} (confirmative) were defined. Artesunate plasma concentrations were analysed in the same way, however with a descriptive intention, only. Noncompartmental PK parameters of artesunate and DHA were derived from each individual plasma concentration versus time profile using standard methods.

The main noncompartmental PK parameters for DHA following single administration of 4x50mg and 200mg artesunate are presented in table 6 below.

Parameter / Formulation for dihydroartemisinin	TEST (N = 24) (4 x 50 mg)	REFERENCE (N = 24) (200 mg)
AUC0-∞ [h·ng/ml]	1504.95 ± 405.44 (1553.44) [1333.75 – 1676.15]	1322.25 ± 451.11 (1313.31) [1131.76 – 1512.74]
%AUC [%]	1.88 ± 0.80 (1.64) [1.55 – 2.22] Max: 3.94	2.75 ± 3.01 (1.99) [1.48 – 4.02] Max: 15.57
AUC0-tlast [h·ng/ml]	1478.18 ± 403.98 (1516.18) [1307.59 – 1648.77]	1292.30 ± 453.32 (1291.90) [1100.88 – 1483.73]
Cmax [ng/ml]	975.58 ± 489.44 (895.50) [768.91 – 1182.26]	861.21 ± 491.66 (739.50) [653.60 – 1068.82]
$t_{1/2}$[h]	1.12 ± 0.19 (1.08) [1.04 – 1.21]	1.12 ± 0.32 (1.03) [0.99 – 1.26]
tmax [h]	1.08 ± 0.77 (0.88) [0.75 – 1.40]	1.22 ± 0.67 (1.13) [0.93 – 1.50]

Table 6: Arithmetic mean with standard deviation, median values () and 95% confidence intervals [ ] of the main noncompartmental PK parameters for DHA following single administration of 4x50mg and 200mg artesunate (N=24)

The results of the prospectively defined statistical analysis regarding the decision on equivalence are shown in Table 7.

Dihydroartemisinin Pharmacokinetic Characteristics (P = primary, S = secondary)	Test / Reference Point Estimator	Shortest 90% confidence interval	Decision on bioequivalence
P: $AUC_{0\text{-tlast}}$ [h* ng/ml] n=23	111.41 %	[102.36 % - 121.26 %]	Equivalent
P: C_{max} [ng/ml]	116.50 %	[96.98 % - 139.95 %]	equivalent with expanded range 70 % - 143 %
P: $AUC_{0\text{-}\infty}$ [h* ng/ml] n=23	110.67 %	[101.72 % - 120.42 %]	Equivalent
	Test - Reference Point estimator	**Non-parametric 90% confidence interval**	
S: tmax [h]	-0.158 h	[-0.408 h - 0.092 h]	Acceptable

Table 7: Summary of the statistical analysis of the single-dose primary (P) and secondary (S) PK parameters for DHA following administration of 4x50mg versus 200mg artesunate (n=23, excluding one outlier)

Based on the DHA comparison of dosage forms, equivalence between the two tablet forms (containing 50mg and 200mg artesunate) can be concluded regarding the extent and rate of absorption. For the rate of absorption (C_{max}) the expanded acceptance range of 70% - 143% was used as specified in the study protocol.

For statistical evaluation of the dose dependency of the pharmacokinetics, dose linearity was investigated by comparing the PK DHA parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} of the administration of 50 mg versus 200 mg artesunate (table 8). With the dose-normalized parameters an analysis of variance (ANOVA) was performed. This analysis revealed no difference and therefore, linear pharmacokinetics could be concluded in the dose range of 50mg to 200mg artesunate, administered by the oral route in the fasting state.

Dihydroartemisinin Pharmacokinetic Characteristics (P = primary, S = secondary)	Comparison Intercept P - value	Significance
S: AUC0-tlast[h*ng/ml]	0.1306	not significant
S: Cmax[ng/ml]	0.7478	not significant
S: AUC0-∞[h*ng/ml]	0.1643	not significant

Table 8: Summary of the statistical analysis of the single-dose PK parameters for DHA following single administration of 4x50mg versus 200mg artesunate for dose-dependency with the Regression analysis of parameters (N=24)

Analysis of the artesunate plasma concentrations was done with a descriptive intention, since the half-life of artesunate and the appearance of artesunate in plasma are very short resulting in quite pronounced variability. However, the analysis done for the artesunate pharmacokinetics supports the conclusions of the DHA PK analysis, i.e., that both dosage strengths are equivalent and dose-proportionality of the pharmacokinetics of artesunate in the dose-range of 50mg to 200mg of artesunate can be concluded.

2.7.1.2.4 Pharmacokinetic characteristics of two oral paediatric formulations of Artequin

SPC 25-21 / AM-P 001-2005
A clinical study on a paediatric population in Gabon was performed to investigate safety, efficacy, and pharmacokinetic properties of Artequin Paediatric and Artequin 300/750 in a 3-day treatment of children. The efficacy and safety parts of the study are described later in this "Clinical Summary".

71 children with uncomplicated *Plasmodium falciparum* malaria were stratified in two body weight groups, 10 to 20 kg and >20 to 40 kg, respectively.

Each patient with a body weight of 10-20 kg (n = 41) received the medication "Artequin Paediatric Stickpack" once daily for 3 days (Group A). Each patient with a body weight of >20 to 40 kg (n = 30) received the medication "Artequin 300/750", a co-blister formulation of artesunate 100mg and mefloquine 250mg once daily for 3 days (Group B).

To bring efficacy parameters in relation to the PK characteristics of both Artequin Paediatric and Artequin 300/750, plasma concentrations of dihydroartemisinin (DHA) and mefloquine taken at defined time points were investigated.

The plasma concentrations were assessed from individual plasma samples of all patients included in the Pharmacokinetic (PK) assessment (i.e. the first 12 children in each group eligible for PK analysis). Plasma samples for analysis of DHA were taken at day 1 (pre-dose, 0.5, 1, 1.5, 2, 4 and 6 hours after medication) and for the analysis of mefloquine at day 1 (pre-dose and 6 hours after medication), day 3 (6 hours after last medication) and at the Follow-up visit on day 28. For day 1, a blood sampling scheme was chosen to allow demonstration of a complete pharmacokinetic profile of DHA. The average plasma levels reached at specific time points after drug administration are of importance for initial quick start of parasite clearance. Using the 6 hours sampling for DHA, mefloquine sampling was taken in parallel. This on the one hand reduced the invasive stress to the small children, on the other hand allowed an estimate of the mefloquine plasma levels reached at the time when most of the DHA was eliminated from the blood again. Further DHA sampling was not judged essential, since similar DHA profile as for day 1 could be expected again for days 2 and 3.
Due to the long half life of mefloquine, however, for practical and ethical reasons a sparse sampling was defined. Sampling of day 2 was not planned since with the second dose a further increase of plasma levels could be expected. On day 3, one sampling was defined 6 hours after drug administration again to be in line with the reasons of the time point selection for day 1. Last mefloquine blood sampling on day 28 was chosen to demonstrate the remaining blood concentrations at the end of the study period.
This sampling scheme accepted a limitation of the pharmacokinetic assessment due to the fact that the sampling time of 6 hours only comes close to the lower range of t_{max} (8 to 16 hours) and therefore, a C_{max} lower than really reached would be shown. The limited number of samples planned per protocol did not allow formal calculation of mefloquine non-compartmental PK parameters. Thus, only demonstration of the average plasma levels reached at specific time points could be envisaged.

Dihydroartemisinin (DHA) plasma concentrations

Pharmacokinetic parameters are summarized in table 9 below:

Treatment Group	Parameter	N	Arithmetic mean	CV%	Min	Median	Max	Lower 95% CL	Upper 95% CL
A	$AUC_{(0\text{-}inf)}$ (h·ng/ml)	9	3157.86	49.63	1399.5	3024.3	6679.3	1953.25	4362.47
	$AUC_{(0\text{-}tlast)}$ (h·ng/ml)	12	2421.97	70.36	130.5	2050.0	6640.6	1339.25	3504.70
	C_{max} (ng/ml)	12	1181.08	82.97	130.0	861.0	3390.0	558.45	1803.72
	$t_{1/2}$ (h)	9	1.06	46.52	0.6	0.9	2.2	0.68	1.43
	t_{max} (h)	12	2.55	82.71	1.0	1.5	6.1	1.21	3.89
B	$AUC_{(0\text{-}inf)}$ (h·ng/ml)	11	3143.33	61.53	1049.3	2815.0	7791.2	1844.05	4442.62
	$AUC_{(0\text{-}tlast)}$ (h·ng/ml)	12	2427.32	49.08	965.4	2470.1	4781.3	1670.43	3184.21
	C_{max} (ng/ml)	12	1080.50	61.52	286.0	930.0	2190.0	658.12	1502.88
	$t_{1/2}$ (h)	11	1.85	149.24	0.6	1.0	10.1	0.00	3.71
	t_{max} (h)	12	1.57	63.10	0.5	1.5	4.1	0.94	2.19

Table 9: Statistics for selected DHA noncompartmental PK parameters after formulation A (Artequin Pediatric) or formulation B (Artequin 300/750) in children with uncomplicated P. falciparum malaria.

Overall, the mean and median plasma DHA concentrations appear very similar between both formulations in their respective body weight groups. The observed C_{max} values are well above the published in vitro dihydroartemisinin IC_{50} values for *Plasmodium falciparum*.

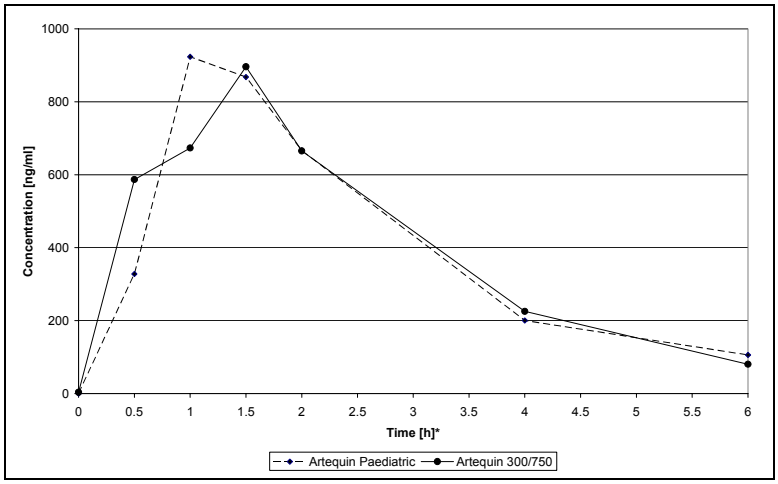

Figure 1: Mean plasma DHA concentration vs. time plot after formulation A (Artequin Paediatric) or formulation B (Artequin 300/750)

As shown in figure 1, the mean DHA plasma concentration-time profiles of DHA in the PK population after the administration of each formulation (Artequin Paediatric and Artequin 300/750) to its respective target population are similar.

Mefloquine plasma concentrations

As explained above, in these very small children only a limited number of mefloquine blood samples were taken (enough to demonstrate the average plasma levels reached at specific time-points but not allowing the formal calculation of PK parameters, see figure 2). The mean mefloquine plasma concentrations 6 hours after the administration of the first dose of each formulation to its respective target population are similar. However, the mean maximum observed value (observed 6 hours after dosing on day 3) appears lower after Artequin 300/750 given to children weighing 20-40 kg (group B). Values at the end of the observation period, however, are higher in treatment group B (mean (SD), 337.33(117.58) ng/ml as compared to 239.23(132.8) ng/ml in group A).

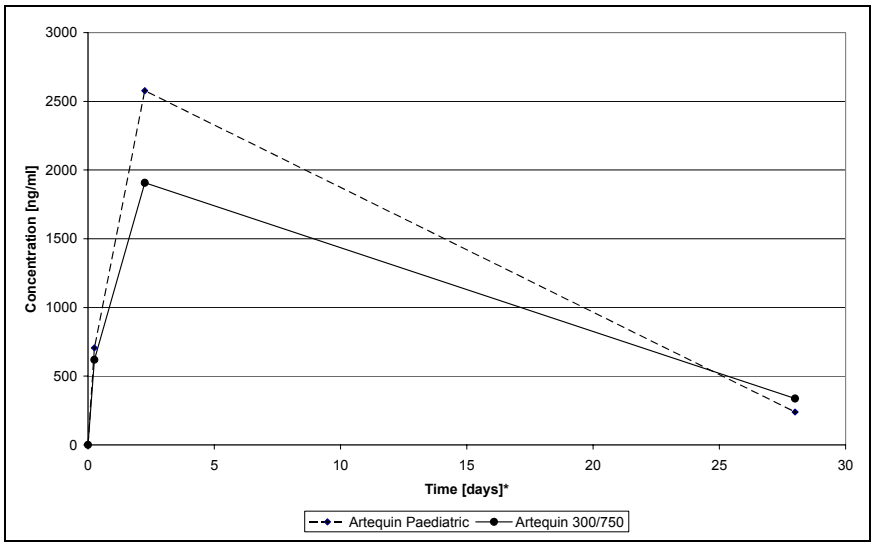

Figure 2: Mean concentration vs. time plot for mefloquine after formulation A (Artequin Paediatric) or formulation B (Artequin 300/750) in children with uncomplicated falciparum malaria.

These pharmacokinetic results are generally in line with the published data (see "Clinical Overview") and allow to conclude - within the limitations of the sample size and the sparse sampling schedule used for mefloquine - that appropriate drug plasma concentrations for the treatment of Plasmodium falciparum infection were reached.

2.7.1.3 Comparison and Analyses of Results Across Studies

Summary PK results are presented in tables 10 and 11.

PK results of studies with healthy volunteers

Study ID	Administration	Measured parameter	AUC_{0-inf} [ng/mLxh]	AUC_{0-t} [ng/mLxh]	C_{max} [ng/mL]	T_{max} [h]	$T_{1/2}$ [h]
Mefloquine alone							
CS 111	Test	Mef	530388.9 ±151339.8	504699.5 ±141562.5	1372.9 ±322.8	6.0 (a)	440.7 ±74.1
CS 111	Reference	Mef	522581.7 ±167466.8	497038.6 ±155851.8	1314.9 ±299.5	6.0 (a)	440.2 ±68.4
Artesunate alone							
SPC 25-16	A	DHA	222.79 ±243.22	205.37 ±242.18	190.26 ±170.56	1.06 ±0.55	0.73 ±0.59
SPC 25-16	B	DHA	1504.95 ±405.44	1478 ±403.98	975.58 ±489.44	1.08 ±0.77	1.12 ±0.19
SPC 25-16	C	DHA	1322.25 ±451.11	1292.30 ±453.32	861.21 ±491.66	1.22 ±0.67	1.12 ±.032
Mefloquine and Artesunate							
ART-INT-01-2005	A (day 3)	DHA	1414 ±383	1382 ±384	680 ±222	0.75 ±0.42	1.09 ±0.33
ART-INT-01-2005	B (day 3)	DHA	1402 ±607	1371 ±609	660 ±313	0.92 ±0.47	1.09 ±0.41
ART-INT-01-2005	B	Mef	ND	101885 ±49371	ND	ND	ND

Table 10:
Mef= Mefloquine; DHA=Dihydroartemisinin; ND=not done
(a) Value presented as median

Study ART-INT-01-2005: Period A was with artesunate alone. Therefore no mefloquine measurements. Only AUC0-inf for mefloquine has been calculated for period B because of limited data.

PK results of studies with malaria patients

Study ID	Administration	Measured parameter	AUC_{0-inf} [ng/mLxh]	AUC_{0-t} [ng/mLxh]	C_{max} [ng/mL]	T_{max} [h]	$T_{1/2}$ [h]
Mefloquine and Artesunate							
SPC 25-21	A	DHA	3157.86	2421.97	1181.08	1.5 (a)	0.9 (a)
SPC 25-21	B	DHA	3143.33	2427.32	1080.50	1.5 (a)	1.0 (a)
SPC 25-21	A	Mef	ND	ND	ND	ND	ND
SPC 25-21	B	Mef	ND	ND	ND	ND	ND

Table 11:
Mef= Mefloquine; DHA=Dihydroartemisinin; ND=not done
(a) Value presented as median

Study SPC 25-21: For ethical reasons in the study population of very small children only a limited number of mefloquine blood samples have been taken. This was enough to demonstrate the average plasma levels reached at specific time points but not allowing the formal calculation of PK parameters.

PK results of studies in malaria patients are further discussed in the Clinical Overview, section 2.5.3.2.

Section 2.7.1.4 Appendix

Overview on Pharmacology Studies in healthy volunteers

Study ID	No. of centers	Study Design	Study objective(s)	No. of patients entered/ completed	Dosage regimen
Mefloquine					
CS 111	1	Open-label, randomized, cross-over, single-dose	To assess the relative bioavailability of a new formulation of mefloquine to the innovator product Lariam	Entered 40 Completed 38	Test administration: 3 tablets of Mephaquin Lactab (mefloquine) (3 x 250 mg) Reference administration: 3 tablets of Lariam (mefloquine) (3 x 250 mg)
Artesunate					
SPC 25-16	1	Open-label, randomized, single-dose, 3-way cross-over	To investigate the bioequivalence of two dosage forms of artesunate To investigate the dose proportionality of artesunate pharmacokinetics	Entered 24 Completed 24	Test administrations: - Administration A: 1 x 50 mg artesunate tablet, Mepha - Administartion B: 4 x 50 mg artesunate tablet, Mepha AG Reference administration: - Administration C 1 x 200 mg artesunate tablet, Mepha
Mefloquine/Artesunate					
ART-INT-01-2005	1	Open-label, multiple-dose, 1 sequence cross-over	To investigate possible pharmacokinetic interaction between artesunate and mefloquine	Entered 21 Completed 20	Period A: 1 tablet artesunate 200 mg daily on 3 consecutive days Period B: 1 tablet artesunate 200 mg and 1 tablet mefloquine 250 mg daily on 3 consecutive days

Table 12: Overview on Pharmacology Studies in healthy volunteers

Overview on Pharmacology Studies in patients with malaria

Study ID	No. of centers	Study Design	Study objective(s)	No. of patients entered/ completed	Dosage regimen
Mefloquine/Artesunate					
SPC 25-21*	2	Open-label, stratified	Primary:* To investigate the efficacy as assessed by the 28-day cure rate Secondary: To investigate several efficacy parameters in relation to the blood concentrations of DHA and mefloquine at defined time points.	Entered 71 (24 for PK) Completed 68 (for efficacy), 71 (for safety), 24 (for PK)	Treatment A: A stickpack containing 50 mg artesunate and 125 mg mefloquine Treatment B: Artequin 300/750 1 tablet artesunate 100 mg and 1 tablet mefloquine 250 mg Administration: The investigational therapy consisted of a daily dose of artesunate ranging from 2.5 to 5 mg/kg/day and a daily dose of mefloquine ranging from 6.25 to 12.5 mg/kg/day given simultaneously once daily over 3 days.

Table 13: Overview on Pharmacology Studies in malaria patients

* For details on the efficacy and safety evaluations see section "2.7.3 SUMMARY OF CLINICAL EFFICACY" "2.7.4 SUMMARY OF CLINICAL SAFETY"

2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

2.7.2.1 Background and Overview

Four studies have been presented in the previous section of this Clinical Summary. In all of those studies human pharmacokinetics (and pharmacodynamics) have also been investigated. However, in order to improve the legibility of this document, the PK and PD parts have already been presented in the last section and will not be repeated in this section.

2.7.2.2 Summary of Results of Individual Studies

See previous section 2.7.1.

2.7.2.3 Comparison and Analyses of Results Across Studies

See previous section 2.7.1.

2.7.2.4 Special Studies

Not applicable

Section 2.7.2.5 Appendix

Not applicable

2.7.3 SUMMARY OF CLINICAL EFFICACY

2.7.3.1 Background and Overview of Clinical Efficacy

3 efficacy and safety studies have been conducted. Efficacy results of the studies are presented in this section. Safety is presented in the next section.

Study code	Study title	Study design
AM 001-2001	Randomized, double-blind study on the efficacy and safety of artesunate and mefloquine (Artequin®) given simultaneously for 3 days compared to a sequential treatment in uncomplicated Plasmodium falciparum malaria.	Double-blind, randomized, parallel-group study
AM 002-2001	Randomized, double-blind study on the efficacy and safety of artesunate and mefloquine (Artequin®) given simultaneously for 3 days compared to a sequential treatment in uncomplicated Plasmodium falciparum malaria in Africa.	Double-blind, randomized, parallel-group study
AM-P 001-2005/ SPC 25-21	Open-label, stratified study on the efficacy, safety and pharmacokinetic characteristics of two paediatric formulations of ArtequinTM in children with acute uncomplicated P. falciparum malaria.	Open label

Table 14: Studies presented in this section

In order to improve patient compliance to a combination of artesunate and mefloquine in simultaneous administration and to demonstrate that this therapeutic approach is also valuable for other endemic regions like Africa, the Artequin concept has been developed and clinically investigated. With this approach, artesunate and mefloquine combined in a pre-packed single blister are simultaneously co-administered once daily for 3 days.
Two Artequin phase III studies (AM 001-2001 and AM 002-2001) were performed by Mepha Ltd. The aim of these two studies was to investigate the efficacy and safety of the blister-prepacked artesunate and mefloquine combination, with mefloquine starting already on day 1, administered once daily for a total of 3 days. The regimen was compared to a conventional sequential combination regimen, with the first day of treatment consisting of a single once daily dose of artesunate, followed by 2 days of once daily co-administration of artesunate and mefloquine.

Mepha's new fixed-dose ACT realised in **Artequin Paediatric** contains the higher mean total mefloquine dosage of 25 mg/kg as currently strongly recommended by the WHO for both Asia and Africa. The new concept of Artequin Paediatric has been further investigated in a clinical study (AM-P 001-2005/SPC 25-21).

All studies were done in patients with uncomplicated *Plasmodium falciparum* malaria.

2.7.3.2 Summary of Results of Individual Studies

AM 001-2001
This randomized, double-blind, parallel group, comparative, single center study was conducted in Thailand in 204 adults and children with acute, uncomplicated P. falciparum

malaria. Patients were randomized to two treatment groups and received once daily over three days:
Treatments: Group A: Artesunate 4-5 mg/kg/day (Plasmotrim®-50 or -200 Lactab®) and mefloquine 25 mg/kg (Mephaquin® Lactab®) total dose (≈8.5 mg/kg/day) simultaneously; Group B: artesunate 4-5 mg/kg/day (Plasmotrim®-50 or -200 Lactab) and mefloquine 25 mg/kg (Mephaquin® Lactab®) total dose sequentially (i.e., no mefloquine dose on the first day, 15 mg/kg on the second day and 10 mg/kg on the third day).
Both treatment groups did not relevantly differ as for baseline demographic and clinical characteristics.

For both treatment groups the patients were stratified into 3 different body weight groups:

			Group A		Group B	
Dosing Group	Weight (kg)		Artesunate	Mefloquine	Artesunate	Mefloquine
01	> 50	Day 1 (0 hour)	1 tablet 200 mg	2 tablets 250 mg + 1 placebo tablet	1 tablet 200 mg	3 placebo tablets
		Day 2 (24 hours)	1 tablet 200 mg	2 tablets 250 mg + 1 placebo tablet	1 tablet 200 mg	3 tablets 250 mg
		Day 3 (48 hours)	1 tablet 200mg	2 tablets 250 mg + 1 placebo tablet	1 tablet 200 mg	3 tablets 250 mg
02	36-50	Day 1 (0 hour)	1 tablet 200 mg	2 tablets 250 mg + 1 placebo tablet	1 tablet 200 mg	3 placebo tablets
		Day 2 (24 hours)	1 tablet 200 mg	2 tablets 250 mg + 1 placebo tablet	1 tablet 200 mg	3 tablets 250 mg
		Day 3 (48 hours)	1 tablet 200 mg	1 tablet 250 mg + 2 placebo tablet	1 tablet 200 mg	2 tablet 250 mg + 1 placebo tablet
03	25-35	Day 1 (0 hour)	2 tablets 50 mg	1 tablet 250 mg + 1 placebo tablet	2 tablets 50 mg	2 placebo tablet
		Day 2 (24 hours)	2 tablets 50 mg	1 tablet 250 mg + 1 placebo tablet	2 tablets 50 mg	2 tablets 250 mg
		Day 3 (48 hours)	2 tablets 50 mg	1 tablet 250 mg + 1 placebo tablet	2 tablets 50 mg	1 tablet 250 mg + 1 placebo tablet

Table 15: Dosing scheme based on body weight

Efficacy results: Primary efficacy endpoint was 28-day cure rate (proportion of patients with clearance of asexual parasitemia within 7 days of initiation of study treatment, without subsequent recrudescence within 28 days). Intent To Treat analysis revealed a cure rate at day 28 (primary endpoint) of 100% in group A and 99% in group B (n.s.).
The secondary endpoints mean time to fever clearance (group A 34 h vs. B 31 h) and mean time to parasite clearance (group A 44 h vs. B 48h) were similar between groups (both n.s.).

Conclusion on efficacy: The main outcome of this study was that a 3-day treatment course with artesunate and mefloquine co-administered once daily in identical daily dosages from the first day of therapy is both, highly effective and well tolerated in the treatment of acute, uncomplicated P. falciparum malaria in Thailand. It was as effective and safe as the currently applied sequential artesunate and mefloquine treatment regimen in multidrug-resistant areas in Asia. The age of the patients had no impact on this assessment. Rapid parasite and fever clearances were achieved.

AM 002-2001
A randomised, double-blind, parallel group study in 104 hospitalised patients (weight 30 to 55 kg) with acute, uncomplicated P. falciparum malaria was performed in 3 centers in Africa (Benin, Cameroon and Cote d'Ivoire).

Treatments: Patients were randomised to receive simultaneous dosing of artesunate 200 mg (Plasmotrim®-200 Lactab®) plus mefloquine 250 mg (Mephaquin® Lactab®) from the first to the third day, or sequential dosing [artesunate 200mg/d for three days plus mefloquine 250mg on the second and 500mg on the third day (reference group)]. Patients were followed up for 28 days, and clinical and parasitologic outcomes were assessed.

Efficacy results: Primary efficacy endpoint was the 14-day cure rate (proportion of patients with clearance of asexual parasitaemia within 7 days of initiation of study treatment, without subsequent recrudescence by day 14). The cure rate was 100% in the simultaneous dosing group and 98% in the reference group with no recrudescence until day 14 (ITT population). The results for 28-day cure rates were the same.
Mean times to fever and parasite clearance were similar between the simultaneous dosing group and the reference group (32h VS. 26h and 45h VS. 48h, both n.s.).

Conclusion on efficacy: Efficacy was excellent in both treatment groups with no statistically significant difference between treatment group A and B for any of the evaluated efficacy parameters. The demographic and baseline characteristics as well as the 14- and 28-day cure rates, and the time to parasite and fever clearance were comparable between the two treatment groups.

AM-P 001-2005 / SPC25-21
This was an open-label, stratified study on the efficacy and safety, as well as pharmacokinetic and pharmacodynamic characteristics of the combination of artesunate and mefloquine.
The pharmacokinetic investigations have been presented in the section "2.7.1 SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS".

71 children with uncomplicated malaria, 29 females (40.8%) and 42 males (59.2%), in the age of 1 to 13 years, of Black origin (100% Melano African), with body weight ranging from 10.2 to 39.5 kg were enrolled in this study. 41 children were stratified to treatment group A (children with a body weight of 10.2 to 19.0 kg) and 30 in treatment group B (children with a body weight of 20.3 to 39.5 kg).
The distribution of background characteristics was not comparable between the two groups as they were stratified by body weight. This resulted also in different mean, minimal and maximal values of age and body height between the two treatment groups.

Treatments: Study drug was given daily for 3 days in a fixed-dose combination (Artequin Paediatric Stickpack, 10-20 kg body weight, group A) and in a Co-Blister (Artequin 300/750, >20-40 kg body weight, group B).

Efficacy results: The primary efficacy parameter was the 28-day cure rate, of "Artequin Paediatric Stickpack" and "Artequin 300/750" in a 3-day treatment.

Secondary efficacy parameters included the 14-day cure rate, time to parasite clearance, time to fever clearance, parasite reduction rate during the first 72 hours and evolution of the gametocytemia over time in relation to the blood concentration of dihydroartemisinin (DHA) and mefloquine at defined time points.

Both study treatments showed an appropriate efficacy in the treatment of acute uncomplicated *P. falciparum* malaria as measured by 28-day and 14-day cure rates of 100%, in their respective per protocol target population. The two-sided 95% confidence intervals for the 28-day cure rate were 90.97%-100% and 88.06%-100% for group A and group B respectively.

Treatment Group	28-day cure rate		Two-sided 90% confidence interval		Two-sided 95% confidence interval	
	n	%	Lower limit	Upper limit	Lower limit	Upper limit
A (n=39)	39	100	0.9261	1.000	0.9097	1.000
B (n=29)	29	100	0.9019	1.000	0.8806	1.000
Total (n=68)	68	100	0.9569	1.000	0.9472	1.000

Table 16: 28-day cure rate and confidence intervals (PP-population)
A: Children with body weight of 10 to 20 kg, Artequin Paediatric
B: Children with body weight of >20 to 40 kg; Artequin 300/750

Treatment Group	14-day cure rate		Two-sided 90% confidence interval		Two-sided 95% confidence interval	
	n	%	Lower limit	Upper limit	Lower limit	Upper limit
A (n=39)	39	100	0.9261	1.000	0.9097	1.000
B (n=29)	29	100	0.9019	1.000	0.8806	1.000
Total (n=68)	68	100	0.9569	1.000	0.9472	1.000

Table 17: 14-day cure rate and confidence intervals (PP-population)
A: Children with body weight of 10 to 20 kg, Artequin Paediatric
B: Children with body weight of >20 to 40 kg; Artequin 300/750

Time to parasite clearance was short (median 36.0 h overall and for treatment A, 35.9 h for treatment B) and did not appear to differ greatly. These values appear clinically acceptable for both groups.

The parasite reduction during the first 72 h was appropriate with rates over 90% by day 3 in both groups. In treatment group A, 36 out of 39 (92.3%) patients had negative blood slides for *Plasmodium falciparum* asexual forms as compared to treatment group B (28 out of 29, i.e., 96.6% of patients with negative blood slides).

Body temperature decrease, as measured by the time to fever clearance, was quicker after treatment B (median 12.3 hours) than after treatment A (median 23.3 hours). This can be explained by the presence of more patients with very high parasite counts (>150000 asexual forms/µl) in group A (10/41) than in group B (1/30). Overall, the observed times to fever clearance are clinically acceptable for both treatment groups.

Conclusion on efficacy: Both study treatments (A: Artequin Paediatric; B: Artequin 300/750) showed an appropriate efficacy in the treatment of acute uncomplicated P. falciparum malaria as measured by 28-day and 14-day cure rates of 100% in the PP population in both cases, in their respective target population, children with a body weight of 10 to 20 kg for treatment A and children with a body weight of 20 to 40 kg for treatment B.

2.7.3.3 Comparison and Analyses of Results across Studies

2.7.3.3.1 Study populations

Country	Treatment [arm]	Body weight	Populations			
			Rando-mised/ Enrolled	ITT	PP	Ana-lysable for Safety
AM 001-2001*						
Thailand	Treatment A: Investigational treatment, artesunate/mefloquine "dosed simultaneously"	> 50 kg	62	62	61	62
		36-50 kg	30	30	30	30
		25-35 kg	10	10	9	10
	Treatment B: Reference treatment, artesunate/mefloquine "dosed sequentally"	> 50 kg	62	62	61	62
		36-50 kg	30	30	30	30
		25-35 kg	10	10	10	10
AM 002-2001						
Africa	Treatment A: Investigational treatment, artesunate/mefloquine "dosed simultaneously	30-55 kg	52	52	51	52
	Treatment B: Reference treatment, artesunate/mefloquine "dosed sequentally"	30-55 kg	52	52	47	52
AM-P 001-2005/SPC25-21						
Africa	Treatment A: Artequin Paediatric stickpack	10-20 kg	41	41	39	41
	Treatment B: Artequin 300/750	>20 to 40 kg	30	30	29	30

Table 18: Efficacy/safety studies and their PP, ITT, and Safety populations
* study AM-001-2001: For both treatment groups the patients were stratified according to body weight into 3 subgroups

A total of 379 patients with uncomplicated P. falciparum malaria were enrolled in 3 efficacy/safety studies. All patients received a combination treatment with artesunate and mefloquine. 2 studies were conducted in Africa (175 patients) and one study was done in Thailand (204 patients). The study population consisted of children with a body weight >10 kg and adults. Malaria diagnosis was confirmed by a positive blood smear with asexual forms of *Plasmodium falciparum*.

Two studies were double-blind, randomized. One study was open. A blinded design was not possible because the treatment groups differed in body weight (10-20 kg versus >20 - 40) and received different treatments. The open design does not limit the overall quality of the study as efficacy of malaria treatment is generally based on endpoints that are not subject of biasing (e.g. parasite clearance). "Per protocol" and "Intention to treat" populations were quite similar in all 3 studies. This was achieved by a low number of

patients discontinuing the study which is often a problem in malaria studies, especially for evaluation of cure rate at day 28.

2.7.3.3.2 Comparison of Efficacy Results of all studies

For malaria treatment, some clinical endpoints have been well-defined and based on those endpoints a comparison between studies is possible. Limitations to such a comparison might be different total dosages of mefloquine per body weight and different malaria transmission status (Asia vs Africa).
Here the results of the studies are presented without further explanations. A detailed discussion of all those aspects is presented in the Clinical Overview, section 2.5.4.

Study ID/ Treatment arm	Initial mean parasitemia count [per mm^3 blood]	Mean age [Years] (Range)	14-day cure rate No [%]	28-day cure rate No [%]	Patients with Recru-descence [%]	Mean clearance time [h]	
						fever	Para-sitaemia
AM 001-2001*							
Group A (ITT)	27'624	27.3 (8-63)	102(100)	**102(100)**	0	34.0	44.3
Group B (ITT)	40'045	26.8 (8-60)	101(99)	**101(99)**	1(1)	30.6	47.8
AM 002-2001							
Group A (ITT)	35'700	21.9 (10-64)	**52(100)**	52(100)	0	31.9	45.4
Group B (ITT)	25'937	19.5 (6-57)	**51(98)**	51(98)	1(2)	26.1	48.3
Group A (PP)	-	-	**51(100)**	-	-	-	-
Group B (PP)	-	-	**47(100)**	-	-	-	-
AM-P 001-2005/SPC25-21							
Group A (PP)	72'786	3.8 (1-6)	39 (100)	**39 (100)**	0	21.6	36.6
Group B (PP)	56'651	8.7 (5-13)	29 (100)	**29 (100)**	0	18.4	30.8
Group A (ITT)	-	-	-	**41 (100)**	-	-	-
Group B (ITT)	-	-	-	**30 (100)**	-	-	-

Table 19: Important efficacy results (bold: Primary efficacy parameters)
PP: Per protocol analysis
ITT: Intention to treat analysis
* No PP analysis has been conducted because the number of patients in the PP population deviated less than 5% from the ITT population.

2.7.3.3.3 Comparison of Results in Subpopulations

"Artequin Paediatric Stickpack" is indicated for children with a body weight from 10 to 20 kg. The clinical studies presented so far in this Clinical Summary were designed with the objective to investigate paediatric subpopulations. Study AM-P-001-2005/SPC25-21 has

investigated efficacy of an "Artequin Paediatric Stickpack" treatment in a population of children with a body weight of 10 to 20 kg. The results have been presented before.
In study AM-001-2001 the patients were stratified in both treatment arms into 3 different body weight groups. One group was a paediatric group consisting of children with 25 to 35 kg body weight. Demographic data are presented in the next table 20.

	Treatment					
	A (n=102)			**B (n=102)**		
	Dosing group			**Dosing group**		
	25-35 kg (n=10)	**36-50 kg (n=30)**	**›50kg (n=62)**	**25-35 kg (n=10)**	**36-50 kg (n=30)**	**›50kg (n=62)**
Sex - n (%)						
Male	9 (90.0)	20 (66.7)	50 (80.6)	5 (50.0)	20 (66.7)	52 (83.9)
Female	1 (10.0)	10 (33.3)	12 (19.4)	5 (50.0)	10 (33.3)	10 (16.1)
Race - n (%)						
Oriental/asian	10 (100)	30 (100)	62 (100)	10 (100)	30 (100)	62 (100)
Mean Age (yr)	10.8	26.1	30.5	11.3	24.2	30.6
SD	1.3	12.1	10.5	1.6	11.8	9.8
range	9-13	8-63	12-58	8-14	11-54	17-60
Mean weight (kg)	27.2	44.7	57.5	28.9	45.4	57.5
SD	3.1	4.0	6.1	3.8	3.1	6.1
range	25.0-35.0	36.0-49.9	50.0-75.0	25.0-35.0	39.0-49.5	57.0-75.0
Mean height (cm)	134.5	155.4	164.7	141.9	156.9	164.7
SD	7.3	7.8	7.0	9.4	7.2	6.7
range	126.0-150.0	136.0-168.0	150.0-181.0	132.0-165.0	143.0-173.0	150.0-181.0

Table 20: Study AM-001-2001. Demographic data of dosing groups stratified to body weight

Here the efficacy results (14 and 28-day cure rate) for each stratum are presented in tables 21 and 22.

	Treatment					
	A (n=102)			**B (n=102)**		
	Dosing Group			**Dosing Group**		
	> 50kg (n=62)	**36-50kg (n=30)**	**25-35kg (n=10)**	**> 50kg (n=62)**	**36-50kg (n=30)**	**25-35kg (n=10)**
28-day cure rate –n (%)	62 (100)	30 (100)	10 (100)	62 (100)	29 (96.7)	10 (100)

Table 21: Study AM-001-2001. 28-day cure rates of dosing groups stratified to body weight

	Treatment							
	A (n=102)				**B (n=102)**			
	Dosing group				**Dosing group**			
	> 50kg (n=62)	**36-50 kg (n=30)**	**25-35 kg (n=10)**	**Pooled**	**> 50kg (n=62)**	**36-50 kg (n=30)**	**25-35 kg (n=10)**	**Pooled**
14-day cure rate –n (%)	62 (100)	30 (100)	10 (100)	**102 (100)**	62 (100)	29 (96.7)	10 (100)	**101 (99.02)**

Table 22: Study AM-001-2001. 14-day cure rates of dosing groups stratified to body weight

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

The rationale for the Artequin dosage strengths in relation to the patient's body-weight ranges is discussed in the Clinical Overview, section 2.5.4.2.4.

2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

The 3 efficacy/safety studies were conducted with a 3-day treatment scheme. Persistence of efficacy was investigated until 28 days after initiation of treatment and was very good. As 28-day cure rate is a generally accepted efficacy endpoint no further investigations with longer time-periods were done.

Tolerance effects are not described to our knowledge for artesunate or mefloquine and have not been investigated throughout this clinical program.

Section 2.7.3.6 Appendix

General study design

No. of centers	Study Design	Study objective(s)	Patients
AM 001-2001			
1 (Thailand)	Randomized, double-blind, parallel-group study	P: To compare the efficacy of the combination of artesunate and mefloquine given simultaneously versus a conventional regimen of the combination of artesunate and mefloquine given sequentially S: Safety and tolerability and further efficacy parameters	Adults and children with a body weight over 25 kg with uncompli-cated *Plasmodium falciparum* Malaria Entered: 204 (102 in each group) Completed: 204
AM 002-2001			
3 (Benin, Cameroon, Ivory Coast)	Randomized, double-blind, parallel-group study	P: To compare the efficacy of the combination of artesunate and mefloquine given simultaneously versus a conventional regimen of the combination of artesunate and mefloquine given sequentially S: Safety and tolerability and further efficacy parameters	Adults and children with a body weight between 30 and 55 kg with uncomplicated *Plasmodium falciparum* Malaria Entered: 104 (52 in each group) Completed: 101
AM-P 001-2005/SPC25-21			
2 (Gabon)	Open label	P: To investigate the efficacy, as assessed by the 28-day cure rate, of Artequin Paediatric and Artequin 300/750 in a 3-day treatment of children (stratified in two body weight groups, 10 to 20 kg and >20 to 40 kg, respectively) with uncomplicated Plasmodium falciparum malaria. S: To investigate other efficacy parameters like the 14-day cure rate, time to parasite clearance, time to fever clearance, parasite reduction rate during the first 72 hours and evolution of the gametocytemia over time in relation to the blood concentration of dihydroartemisinin (DHA) and mefloquine at defined time points, of Artequin Paediatric and Artequin 300/750 in a 3-day treatment of children (stratified in two body weight groups, 10 to 20 kg and >20 to 40 kg, respectively) with uncomplicated Plasmodium falciparum malaria. To evaluate the safety, tolerability and acceptability of drug intake of Artequin Paediatric and Artequin 300/750 in a 3-day treatment of children (stratified in two body weight groups, 10 to 20 kg and >20 to 40 kg, respectively) with uncomplicated Plasmodium falciparum malaria.	Children with a body weight between 10 and 40 kg with uncomplicated *Plasmodium falciparum* Malaria Entered: 71 (52 in each group) Completed: 68

Table 23: Efficacy/safety studies and general study design
P=Primary objective, S=Secondary objective

Treatments administered

Treat-ment [arm]	Total dosages (over 3 days) for artesunate and mefloquine acc. to protocol	Dose regimen	Formulations
AM 001-2001 (Thailand)			
Investig. A	Body weight > 50 kg: - 600 mg artesunate - 1500 mg mefloquine	Total dose of artesunate and mefloquine divided equally over 3 days =Simultaneous treatment	Artesunate: Plasmotrim® 50 Lactab®, Plasmotrim® 200 Lactab®, Mepha Ltd. Mefloquine: Mephaquin® 250 Lactab®
	Body weight 36-50 kg: - 600 mg artesunate - 1250 mg mefloquine		
	Body weight 25-35 kg: - 300 mg artesunate - 750 mg mefloquine		
Ref. B	Body weight > 50 kg: - Same dosages as for investigational treatment	Total dose of artesunate divided equally over 3 days No mefloquine on the first day, 15 mg/kg on the 2nd day and 10 mg/kg on the 3rd day =Sequential treatment	
	Body weight 36-50 kg: - Same dosages as for investigational treatment		
	Body weight 25-35 kg: - Same dosages as for investigational treatment		
AM 002-2001 (Africa)			
Investig. A	Body weight 30 to 55 kg: - 600 mg artesunate - 750 mg mefloquine	Total dose of artesunate and mefloquine divided equally over 3 days =Simultaneous treatment	Artesunate: Plasmotrim® 200 Lactab®, Mepha Ltd. Mefloquine: Mephaquin® 250 Lactab®
Ref. B	Body weight 30 to 55 kg: - 600 mg artesunate - 750 mg mefloquine	Total dose of artesunate divided equally over 3 days No mefloquine on the first day, 250 mg on the 2nd day and 500 mg on the 3rd day =Sequential treatment	
AM-P 001-2005/SPC25-21 (Africa)			
Treat-ment A	Body weight 10 to 20 kg: - 150 mg artesunate - 375 mg mefloquine	Total dose of artesunate and mefloquine divided equally over 3 days	Artequin Paediatric Stickpack
Treat-ment B	Body weight 20 to 40 kg: - 300 mg artesunate - 750 mg mefloquine	Total dose of artesunate and mefloquine divided equally over 3 days	Artequin 300/750 = 3 tablets of artesunate 100 mg and 3 tablets of mefloquine 250 mg

Table 24: Efficacy/safety studies and treatments administered

2.7.4 SUMMARY OF CLINICAL SAFETY

2.7.4.1 Exposure to the Drug

2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

All 6 studies presented in this Clinical Summary have been conducted with evaluation of safety relevant results ("Total safety population", table 25).

Study code	Study title	Total safety population	Effective safety population
1) CS 111	Relative bioavailability of a new tablet formulation of MEPHAQUIN LACTABS® from Mepha Ltd. and LARIAM® from Hoffmann-La Roche Ltd. under fed conditions in healthy volunteers.	40 Healthy volunteers	-
2) ART-INT-01-2005	An assessment of the pharmacokinetic interaction between artesunate and mefloquine in healthy Caucasian volunteers.	21 Healthy volunteers	-
3) SPC 25-16	Randomized, single-dose, 3-way cross-over study to investigate the bioequivalence of two dosage forms of artesunate and to investigate the dose proportionality of artesunate pharmacokinetics (Plasmotrim™ Lactab™ oblong).	24 Healthy volunteers	-
4) AM 001-2001	Randomized, double-blind study on the efficacy and safety of artesunate and mefloquine (Artequin®) given simultaneously for 3 days compared to a sequential treatment in uncomplicated Plasmodium falciparum malaria.	204 Malaria patients	204 Malaria patients
5) AM 002-2001	Randomized, double-blind study on the efficacy and safety of artesunate and mefloquine (Artequin®) given simultaneously for 3 days compared to a sequential treatment in uncomplicated Plasmodium falciparum malaria in Africa.	104 Malaria patients	104 Malaria patients
6) AM-P 001-2005/ SPC 25-21	Open-label, stratified study on the efficacy, safety and pharmacokinetic characteristics of two paediatric formulations of Artequin™ in children with acute uncomplicated P. falciparum malaria.	71 Malaria patients	71 Malaria patients
Total		**464**	**379**

Table 25: Studies presented in this section: Studies 1-3 are only presented to a very limited extend

However the first 3 studies are not reflecting the safety profile of Artequin Paediatric because studies 1 and 3 were conducted with either artesunate or mefloquine alone and furthermore, the first 3 studies presented in the table above are bioavailability/bio-equivalence studies and the safety data is from small populations of healthy volunteers. For those 3 studies a short narrative is given and a summary table on the adverse events is presented in the appendix of this section but the studies are not further mentioned or discussed in this section. The focus of this section is on the studies 4 to 6 (effective safety population).

The narratives of the studies have already been given in sections 2.7.1 "SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS" and 2.7.3 "SUMMARY OF CLINICAL EFFICACY". The narratives of the studies presented below in this section are a brief summary on safety population, drug exposure and safety measurements.

1) CS 111
40 healthy volunteers received 3 tablets (single dose) of the test drug (total of 750 mg mefloquine) and single dose 3 tablets of the reference drug (total 750 mg mefloquine) in a cross-over design. There was a 9-week washout period between the two drug intakes.

38 subjects took the study medication as defined. One subject did not take the reference drug and another subject did not take the test drug. All 40 subjects were included in the safety analysis.

Adverse events, vital signs (blood pressure and heart rate), clinical laboratory test and 12 -lead ECG were recorded during the screening period (for baseline evaluation) and at the follow-up check (24 h after the last drug administration). In addition, ECG's, adverse events and vital signs were recorded at various time points before and after dosing.

2) ART-INT-01-2005
21 healthy volunteers received during period A 1 tablet artesunate 200 mg daily on 3 consecutive days and during period B 1 tablet artesunate 200 mg and 1 tablet mefloquine 250 mg daily on 3 consecutive days. A wash-out period of 21 days was implemented between period A and B.

All 21 subjects took the study drugs as defined.

Adverse events, clinically significant deviations from laboratory tests, physical examinations, and vital signs were recorded throughout the study.

3) SPC 25-16
24 healthy subjects received single-dose artesunate in a 3-way cross-over study. The dosages were one tablet of artesunate 50 mg (administration A), 4 tablets of artesunate 50 mg (administration B), and one tablet of artesunate 200 mg (administration C).

All 24 subjects completed the study according to protocol.

Safety measurements (ECG, vital signs, blood chemistry and haematology) were conducted before and after the study, adverse events were monitored throughout the study.

4) AM 001-2001

This randomized, double-blind, parallel group, comparative, single center study was conducted in Thailand in 204 adults and children with acute, uncomplicated P. falciparum malaria.

Evaluation of safety and tolerability of an artesunate/mefloquine combination was one of the secondary objectives of the study.

Dosing of study drugs and study populations:

Patients were randomized to two treatment groups and received once daily over three days:

- Group A: Artesunate 4-5 mg/kg/day (Plasmotrim®-50 or -200, Lactab®) and mefloquine 25 mg/kg (Mephaquin® Lactab®) total dose (-8.5 m~/kg/day) simultaneously
- Group B: Artesunate 4-5 mg/kg/day (Plasmotrim®-50 or -200, Lactab®) and mefloquine 25 mg/kg (Mephaquin® Lactab®) total dose sequentially (i.e., no mefloquine dose on the first day, 15 mg/kg on the second day and 10 mg/kg on the third day).

For both treatment groups the patients were stratified into 3 different body weight groups and the total dosage of artesunate and mefloquine was adapted to the body weight (see section 2.7.3.2 Summary of Results of Individual Studies) for detailed dosing.

The effective drug disposition per kg body weight for artesunate and mefloquine is presented in table 28.

All 102 patients (100%) of treatment group A took the study medication according to the protocol (i.e. for three consecutive days and according to the stratified dosing scheme. One patient (17/TA), randomized to treatment B in dosing group > 50 kg discontinued the study medication after the first dose on day 1. This patient experienced a Serious Adverse Event. All other 101 patients of treatment group B took the study medication according to the protocol (i.e. for three consecutive days) and according to the stratified dosing scheme.

Two patients, randomized to group A, experienced vomiting within 30 minutes after intake of study drug on day 1. For both patients the full dose of study drug was replaced. No other patient in this group vomited on Day 2 or Day 3.

No patients experienced vomiting within 31 to 60 minutes after intake of study medication at any of the three days.

	Treatment A			Treatment B		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Vomiting within 30 min.	2 (2.0)	0	0	0	0	0
Vomiting within 31 and 60 min.	0	0	0	0	0	0
Full dose replaced	2 (2.0)	0	0	0	0	0
Half dose replaced	0	0	0	0	0	0

Table 27: Patients with vomiting

Safety and tolerability assessments:

All randomised patients were evaluated for safety. Safety assessment consisted of monitoring and recording of all adverse events and serious adverse events. The regular monitoring of haematology, blood chemistry and urine values, regular measurement of vital signs, and performance of physical examinations.

5) AM 002-2001

A randomised, double-blind, parallel group study in 104 hospitalised patients (weight 30 to 55 kg) with acute, uncomplicated P. falciparum malaria was performed in 3 centres in Africa (Benin, Cameroon and Cote d'Ivoire).
Evaluation of safety and tolerability of an artesunate/mefloquine combination was one of the secondary objectives of the study.

Dosing of study drug and study populations:
Patients were randomised to receive:
- "Simultaneous" dosing of artesunate 200 mg (Plasmotrim®-200 Lactab®) plus mefloquine 250 mg (Mephaquin® Lactab®) from the first to the third day (group A), or
- "Sequential" dosing [artesunate 200mg/d for three days plus mefloquine 250mg on the second and 500mg on the third day (group B)].

Three patients discontinued the study before day 28. However this was after they had taken the study drug. 6 patients experienced vomiting within the first 30 minutes after intake of study medication. For all of those patients the full dose was replaced. No patients experienced vomiting within 31 to 60 minutes after intake of study medication at any of the three days. Therefore all patients took the study medication as defined in protocol.

	Treatment A			Treatment B		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Vomiting within 30 min.	1 (1.9)	0	0	1 (1.9)	0	4 (7.7)
Vomiting within 31 and 60 min.	0	0	0	0	0	0
Full dose replaced	1 (1.9)	0	0	1 (1.9)	0	4 (7.7)
Half dose replaced	0	0	0	0	0	0

Table 28: Patients with vomiting

Safety and tolerability assessments:
All randomised patients were evaluated for safety. Safety assessment consisted of monitoring and recording of all adverse events and serious adverse events, the regular monitoring of haematology. Blood chemistry and urine values, regular measurement of vital signs, and performance of physical examinations.

6) AM-P 001-2005/ SPC 25-21

This clinical study on a paediatric population in Gabon was performed to investigate safety, efficacy, and pharmacokinetic properties of Artequin Paediatric and Artequin 300/750 in a 3-day treatment of children with uncomplicated *Plasmodium falciparum* malaria.

Dosing of study drugs and study population: 71 children were stratified in two body weight groups, 10 to 20 kg and >20 to 40 kg, respectively.

Each patient with a body weight of 10-20 kg (n = 41) received the medication "Artequin Paediatric Stickpack" once daily for 3 days (Group A). Each patient with a body weight of >20 to 40 kg (n = 30) received the medication "Artequin 300/750", a co-blister formulation of artesunate 100mg and mefloquine 250mg once daily for 3 days (Group B).

2 patients out of 71 (both in group A) discontinued study medication before day 3.

Safety and tolerability assessments: Safety assessment consisted of monitoring and recording of all adverse events and serious adverse events, the regular monitoring of haematology and blood chemistry, regular measurement of vital signs, performance of physical examinations and a 12-lead ECG at Baseline, day 3 and day 28.

2.7.4.1.2 Overall Extent of Exposure

In June 1998 the WHO published policy guidelines on the use of artesunate and related artemisinin derivatives in combination with mefloquine for the treatment of uncomplicated malaria.
According to these guidelines, artesunate 4 mg/kg once a day for 3 days (12 mg/kg total dose) was to be combined to mefloquine 15 to 25 mg/kg total dose, as a single or split dose on the second or third day.
For non-immune patients living in low transmission endemic area like Thailand, with high incidence of multi-drug resistant strains of P. falciparum, high mefloquine doses were recommended (i.e., 25 mg/kg total dose).
For partially immune patients living in high transmission endemic area like Africa where the sensitivity of P. falciparum to mefloquine is still high and where the gastrointestinal tolerability of mefloquine was thought to be problematic, lower mefloquine doses were recommended (i.e. 15 to 25 mg/kg total dose).

Total dosages of artesunate and mefloquine given to patients in AM-001-2001 and AM-002-2001 reflect the WHO recommendations at this time as can be seen in the table below. The recommendation to split the mefloquine dosage to the second and third day of the treatment was followed for the "reference" arms of both studies (sequential treatment). For the arms with the investigational treatment a "simultaneous" treatment was chosen where mefloquine was given together with artesunate over three days. However the total dose was not different between the 2 treatment arms.

WHO modified treatment recommendations in between the conduction of the studies AM-001-2001 and AM-002-2001 and the more recent study AM-P 001-2005/SPC25-21.
Based on the modified recommendations it was strongly recommended to use the higher mean total mefloquine dosage of 25 mg/kg not only in Asia but to apply this concept also for Africa. Those recommendations were implemented in the study protocol AM-P 001-2005/SPC25-21. This explains why the mefloquine dosage is higher than for the "older" study even if both studies were conducted in African population with partial immunity.

Treat-ment [arm]	Total dosages (over 3 days) for artesunate and mefloquine acc. to protocol	Body weight range acc. to protocol	Body weight Mean Median Min-Max [kg]	Artesunate (effective total dose for 3 days) Mean Min-Max [mg/kg]	Mefloquine (effective total dose over 3 days) Mean Min-Max [mg/kg]
AM 001-2001 (Thailand)					
Investig. A	Body weight > 50 kg: - 600 mg artesunate - 1500 mg mefloquine	> 50 kg*	58.5 57.0 50-75	10.3 8.0-12.0	25.6 20.0-30.0
	Body weight 36-50 kg: - 600 mg artesunate - 1250 mg mefloquine	36-50 kg*	44.7 45.8 36.0-49.9	13.4 12.0-16.7	28.0 25.1-34.7
	Body weight 25-35 kg: - 300 mg artesunate - 750 mg mefloquine	25-35 kg*	27.2 26.3 25.0-35.0	11.0 8.6-12.0	27.6 21.4-30.0
Ref. B	Body weight > 50 kg: - Same dosages as for investigational treatment	> 50 kg*	57.9 57.0 50.0-77.0	10.4 7.8-12.0	25.9 19.5-30.0
	Body weight 36-50 kg: - Same dosages as for investigational treatment	36-50 kg*	45.4 46.0 39.0-49.5	13.2 12.1-15.4	27.5 25.3-32.1
	Body weight 25-35 kg: - Same dosages as for investigational treatment	25-35 kg*	28.9 28.0 25.0-35.0	10.4 8.6-12.0	26.0 21.4-30.0
AM 002-2001 (Africa)					
Investig.	- 600 mg artesunate - 750 mg mefloquine	30-55 kg	46.7 49.8 31.0-55.0	12.8 10.9-19.4	16.1 13.6-24.2
Ref.	- 600 mg artesunate - 750 mg mefloquine		44.9 48.0 30.0-55.0	13.4 10.9-20.0	16.7 13.6-25.0
AM-P 001-2005/SPC25-21 (Africa)					
Treat-ment A	- 150 mg artesunate - 375 mg mefloquine	10-20 kg	14.8 - 10.2-19.0	10.1 7.9-14.7	25.3 19.7-36.8
Treat-ment B	- 300 mg artesunate - 750 mg mefloquine	>20 to 40 kg	26.5 - 20.3-39.5	11.3 7.6-14.8	28.3 19.0-36.9

Table 29: Extent of exposure presented as mg/kg body weight
- Investig. = Investigational drug, Ref. = Reference drug, art=artesunate, Mef=mefloquine
- * Study AM-001-2001. The patients of both treatment arms were stratified to 3 groups according to the body weight

2.7.4.1.3 Demographic and Other Characteristics of Study Population

The 3 efficacy/safety studies were conducted in patients with uncomplicated *P. falciparum* malaria. However the studies were conducted in different countries with different transmission rate of malaria and different immune status of the patients.
One of the studies was conducted in Thailand which is a low transmission endemic area with non-immune patients. Two studies were conducted in Africa being a high transmission area with partially immune patients. The implications of those ethnic factors on the dosing of study drugs have already been discussed in section "2.7.4.1.2 Overall Extent of Exposure".

The whole study population comprised patients with a body weight from 10 to 55 kg. Artequin Paediatric is intended for children and therefore the patient population with a lower body weight ranging from 10 to 40 kg is of special interest. See section "2.7.4.5.1 Intrinsic Factors".

2.7.4.2 Adverse Events

2.7.4.2.1 Analysis of Adverse Events

The whole safety population further discussed consists of 379 patients out of 3 studies.

Study code	Safety population
4) AM 001-2001	204
5) AM 002-2001	104
6) AM-P 001-2005/ SPC 25-21	71
Total	**379**

Table 30: Safety population consisting of the 3 efficacy/safety studies

2.7.4.2.1.1 Common Adverse Events

AM 001-2001

Approximately 1/3 of the patients (32.4%) experienced at least one adverse event (27.5% of patients in group A and 37.3% in group B).

	Treatment		Total
	A (N=102)	B (N=102)	(N=204)
Patients studied			
With at least one AE	28 (27.5)	38 (37.3)	66 (32.4)
With at least one SAE	0	1 (1.0)	1 (0.5)
System Organ Class			
Metabolism and nutritional disorders	16 (15.7%)	19 (18.6 %)	35 (17.2%)
Gastrointestinal disorder	10 (9.8 %)	9 (8.8%)	19 (9.3%)
Nervous system disorders	5 (4.9 %)	9 (8.8%)	14 (6.9%)

Table 31: Number (%) of patients with AEs overall and by most affected system organ class (≥8% for any group)
Group A: "Simultaneous" treatment with artesunate/mefloquine
Group B. "Sequential" treatment with artesunate/mefloquine

Hypokalaemia and headache were the only AE's reported with an incidence > 5%. All other noted adverse events were below 5%. The six most frequent reported adverse events are summarised in the table below.

	Treatment	
	A (N=102)	B (N=102)
Most frequent Aes		
Hypokalaemia	13 (12.7)	19 (18.6)
Headache	4 (3.9)	6 (5.9)
Nausea	2 (2.0)	3 (2.9)
Vomiting	3 (2.9)	2 (2.0)
Diarrhoea	2 (2.0)	2 (2.0)
Pyrexia	2 (2.0)	2 (2.0)

Table 32: Number (%) of patients with most frequent adverse events

AM 002-2001

	Treatment A (N=52)	Treatment B (N=52)	Total (N=104)
Patients studied			
With at least one AE	25 (48.1)	24 (46.2)	49 (47.1)
With at least one SAE	0	0	0
With at least one AE possibly related to study medication	13 (25.0)	14 (26.9)	27 (26.0)
System Organ Class			
Gastrointestinal disorders	9 (17.3)	14 (26.9)	23 (22.1)
General disorders	6 (11.5)	3 (5.8)	9 (8.7)
Nervous system disorders	14 (26.9)	6 (11.5)	20 (19.2)

Table 33: Number (%) of patients with AEs overall and by most affected system organ class (≥10% for any group)
Group A: "Simultaneous" treatment with artesunate/mefloquine
Group B. "Sequential" treatment with artesunate/mefloquine

The most frequent adverse events are summarized in the table below.

The incidence rate of vomiting was statistically significantly higher in treatment group B than in the group A (p=0.014). All other adverse events showed no relevant statistical significant difference in occurrence between treatment groups. Incidence of dizziness was numerically higher in group A than in group B. However, this did not reach statistical significance (p=0.138).

	Treatment A (N=52)	Treatment B (N=52)
Most frequent AEs		
Abdominal pain	5 (9.6)	1 (1.9)
Nausea	2 (3.8)	4 (7.7)
Vomiting	2 (3.8)	10 (19.2)
Asthenia	3 (5.8)	1 (1.9)
Dizziness	9 (17.3)	4 (7.7)
Insomnia	5 (9.6)	3 (5.8)

Table 34: Number (%) of patients with most frequent adverse events

AM-P 001-2005/ SPC 25-21

	Treatment Group		Total
	A (n=41)	B (n=30)	(n=71)
Patients studied	n (%)	n (%)	n (%)
With at least one AE	28 (68.3)	22 (73.3)	50 (70.4)
With at least one SAE	1 (2.4)	0	0
With at least one AE related to study medication	10 (24.4)	15 (50.0)	25 (35.2)
With at least one AE with therapy stop of study medication	0 (0)	0 (0)	0 (0)
With at least one AE with severity 'severe'	2 (4.9)	0 (0)	2 (2.8)
System Organ Class			
Gastrointestinal disorders	9 (22.0)	12 (40.0)	21 (29.6)
Infections and Infestations	9 (22.0)	11 (36.7)	20 (28.2)
Nervous system disorder	5 (12.5)	11 (36.7)	16 (22.5)
Respiratory, thoracic and mediastinal disorders	9 (22.0)	6 (20.0)	15 (21.1)
General Disorders and administration site conditions	7 (17.1)	7 (23.3)	14 (19.7)
Blood and lymphatic system disorders	4 (9.8)	5 (16.5)	9 (12.7)
Investigations	6 (14.6)	2 (6.7)	8 (11.3)

Table 35: Number (%) of patients with AEs overall and by most affected system organ class (≥10% for any group)
Group A: Body weight 10-20 kg. Medication "Artequin Paediatric Stickpack"
Group B: Body weight of >20 to 40 kg. Medication "Artequin 300/750", a co-blister formulation

The most frequently reported adverse events (incidence ≥ 5%) are summarized by event in the table below.

	Treatment Group		
	A (N=41)	B (N=30)	Total (N=71)
Most frequent AEs	n (%)	n (%)	n (%)
Cough	9 (22.0)	6 (20.0)	15 (21.1)
Pyrexia	7(17.1)	6 (20.0)	13 (18.3)
Vomiting	5 (12.2)	7 (23.7)	12 (16.9)
Headache	4 (9.8)	8 (26.7)	12 (16.9)
Diarrhea	6 (14.6)	2 (6.7)	8 (11.3)
Abdominal Pain	1 (2.4)	7 (23.3)	8 (11.3
Dizziness	1 (2.4)	5 (16.7)	6 (8.5)
Trichuriasis	0 (0)	5 (16.7)	5 (7.0)
Anaemia	2 (4.9)	2 (6.7)	4 (5.6)
Eosinophilia	2 (4.9)	2 (6.7)	4 (5.6)

Table 36: Number (%) of patients with most frequent adverse events (≥ 5% in any group)

2.7.4.2.1.2 Deaths

There were no deaths.

2.7.4.2.1.3 Other Serious Adverse Events

There was 1 SAE in study AM 001-2001 and 1 SAE in study AM-P 001-2005/SPC25-21. Both SAE were judged to be unrelated to study medication.

AM 001-2001
Patient (I7/TA), a 33 year old male with falciparum malaria was enrolled in treatment group B. Thirty minutes after the first dose, he presented with a hypovolemic shock probably related to dehydration. Systolic blood pressure was 90 mmHg and the diastolic blood pressure was 60 mmHg. The event was treated with Dopamine. The blood pressure of this patient returned to 97/61mmHg after the symptomatic treatment. on the same day. Study medication was permanently discontinued and the patient completely recovered (after 3 days of symptomatic treatment). The patient received i.v. artesunate as antimalarial rescue therapy.
This SAE was judged to be unrelated to study medication. This SAE was rather related to the underlying malaria infection with dehydration and hypotension.

AM-P 001-2005/SPC25-21
Patient 202/BIN of treatment group A (Artequin Paediatric), a 3 and a half year old child experienced twelve days after the end of the treatment an accident: The child put his left hand in a machine and a finger was broken. The patient was hospitalised for surgery.
The relationship to study drug was judged as “not related”.

2.7.4.2.1.4 Other Significant Adverse Events

In study AM-P 001-2005/SPC25-21 two AE's were rated as severe (both group A). One of them was also serious and has been presented in the previous section. The other patient showed convulsions.
Both AE's were judged not to be related to the study drug.

2.7.4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome

Table 37 shows numbers and percentages of patients with adverse events by most affected system organ class (≥ 8% for any treatment group).

System Organ Class	AM 001-2001*		AM 002-2001**		AM-P 001-2005**	
Group/Period	**A**	**B**	**A**	**B**	**A**	**B**
Gastrointestinal disorders	10 (9.8)	9 (8.8)	9 (17.3)	14 (26.9)	9 (22.0)	12 (40.0)
Infections and Infestations	-	-	-	-	9 (22.0)	11 (36.7)
Nervous system disorder	5 (4.9)	9 (8.8)	14 (26.9)	6 (11.5)	5 (12.5)	11 (36.7)
Respiratory, thoracic and mediastinal disorders	-	-	-	-	9 (22.0)	6 (20.0)
General disorders and administration site conditions	-	-	6 (11.5)	3 (5.8)	7 (17.1)	7 (23.3)
Blood and lymphatic system disorders	-	-	-	-	4 (9.8)	5 (16.5)
Metabolism and nutritional disorders	16 (15.7)	19 (18.6)	-	-	-	-

Table 37: Total numbers of most important adverse events. "Most important" was defined to be > 8%* or 10%** in any group, respectively.

2.7.4.2.2 Narratives

AM 001 2001

The tolerability was very good in both treatment groups and in all dosing groups. One serious adverse event was reported which was judged to be unrelated to study medication but rather due to the malaria infection. Only 1/3 of the patients experienced at least one AE over the course of the study which were considered as non-related to study medication but rather reflecting signs and symptoms of the underlying malaria episode. None of the reported AE showed any relevant statistical significant difference in occurrence between treatment groups. No clinically significant changes of vital signs, laboratory parameters, ECGs were noted during the study.

AM 002-2001

The tolerability was very good in both treatment groups. No SAE have been reported. The incidence of vomiting was statistically significantly lower in the Artequin group (A) as compared to the reference group (B) [3.8% (A) vs 19.2% (B). p=0.014]. The incidence of dizziness [17.3% (A) vs 7.7% (B), n.s.] and CNS side effects in general were comparable between groups. Haematological and biochemical parameters as well as blood pressures were not different between treatment groups.

AM-P 001-2005/SPC 25-21

The overall tolerability of both study formulations appeared appropriate. Most adverse events were of mild to moderate severity. Laboratory findings are in line with those expected in patients suffering from falciparum malaria and tended to improve as long as the study progressed.
Fifty (70.4%) patients experienced at least one adverse event. Twenty-five patients (35.2%) experienced one adverse event judged as related to the study medication, with more treatment group B (50.0%) than treatment group A (24.4%) patients experiencing AEs judged as related to the study medication.
Most AEs were of mild severity, with only a fourth reaching moderate severity. Only 2 patient had AEs rated as severe, one of them reported as serious (required hospitalisation), both in treatment group A (4.9% of group A patients). However, both were judged as not related to the study medication. The most frequently reported AEs were vomiting, abdominal pain, pyrexia, dizziness, and headache that are likely to be part of the falciparum malaria clinical syndrome. The only reported SAE was a traumatic accident leading to a fracture of digitus II, unrelated to the study drug.
Regarding differences between treatment groups, diarrhea was more frequent in group A, probably due to their younger age. Group B patients were more likely to suffer headache, abdominal pain, dizziness and trichiuriasis.

2.7.4.3 Clinical Laboratory Evaluations

Marked laboratory abnormalities and those that led to a substantial intervention have been reported in the sections 2.7.4.2.1.3 and 2.7.4.2.1.4.

In this section (2.7.4.3) some characteristic changes in patterns of laboratory test - usually seen with malaria treatment - are described.

AM-001-2001
Haematological and biochemical parameters were comparable at Baseline, and there were no clinically meaningful trends or differences among the treatment groups for any of the variables at each time point or in changes from baseline.

<u>Haematology</u>
Almost all patients had deviations of their individual laboratory parameters from normality as indicated by the normal ranges given by the laboratory. The abnormal but clinically not significant values of haemolgobin, haematocrit, red blood cell or any white cell counts reflect the underlying malaria infection often associated with anaemia. The haematology laboratory parameters usually returned to normal levels by Day 28. There was no clinically meaningful differences between the 2 treatment groups in the incidence of these changes. Regarding reticulocytes, a comparable decrease in both treatment groups has been observed from Baseline value to Day 7 with a return to normal value by Day 28.

Biochemistry:
Overall there appeared to be no clinically meaningful differences between the treatment groups for the majority of biochemistry parameters.

AM-002-2001

Haematological and biochemical parameters were comparable at Baseline, and there were no clinically meaningful trends or differences among the treatment groups for any of the variables at each time point or in changes from baseline.

Haematology
Most of the patients had abnormal but not clinically significant haematology laboratory parameters at Baseline reflecting the underlying malaria infection often associated with anaemia. Haemoglobin, hematocrit, red blood cell or any white blood cell counts usually returned to normal levels by day 28. There appeared to be no clinically meaningful differences between the 2 treatment groups in the incidence of these changes. Regarding reticulocytes, a comparable decrease in both treatment groups has been observed by Day 4 with a return to Baseline value by Day 28.

Biochemistry
Overall, there appeared to be no clinically meaningful differences between treatment groups for the majority of biochemistry parameters.

AM-P 001-2005/ SPC 25-21
Hematological abnormalities were frequent at baseline. They mostly consisted in decreases in hemoglobin, hematocrit and RBC with increased reticulocytes. Concomitantly, neutrophil percentages tended to be high, eosinophil percentages to be lower than at later timepoints and platelet counts to be low, expected changes in *falciparum* malaria. By day 28, hemoglobin, hematocrit and RBC values are higher, although still lower than expected, reticulocyte percent decreased and platelets increased. These are the expected changes during the recovery of malaria. Eosinophil percent increased and even reach mean values that would be considered abnormal, likely due to the frequent infestations by metazoan parasites in the study population.
Regarding clinical chemistry tests, most abnormalities were not clinically significant. The only significant abnormalities in clinical chemistry were an increase in serum transaminases up to 271.00 UI/L for SGOT as compared to an upper normal limit of 19.00 UI/L and of SGPT up to 197.00 UI/L as compared to an upper normal limit of 23.00 UI/L, peaking on day 3 but present before treatment. 2 cases of increases in plasma triglycerides occurred, in one case reaching a value above 9.03 mmol/l. Although not present at baseline and reverting, the significance of triglyceride increases in samples not obtained under proper fasting conditions is uncertain due to the lack of appropriate reference ranges. Furthermore, isolated increases of triglycerides due to the underlying disease (malaria) are reported in the literature.

2.7.4.4 Vital Signs, Physical Findings, Other Observations Related to Safety

Systolic and diastolic blood pressure, pulse rate, ECG, and temperature were done as vital parameters in the 3 efficacy/safety studies.

The observed abnormalities in vital signs, mostly increased blood pressure and pulse rate, can be expected due to the malarial infection and the hyperdynamic circulatory status induced by the anaemia it induces. In general, they tended to improve along the study, supporting that they were due to the treated condition rather than to the study medication.

Fever clearance has been defined as efficacy parameter and has been described in section 2.5.3 "Summary of clinical Efficacy".

Overall, there were no clinically meaningful trends or differences among the treatment groups for any of the variables at each time point or in changes from baseline.

In study ART-INT-01-2005 the Qtc interval was investigated. All healthy subjects that entered the study received ECG's on study days 1 and 3 of period A (artesunate alone) and on days 1 and 3 of study period B (artesunate and mefloquine). ECG's were taken at 0, 4 and 8 hours on each day.
There was no significant difference on Qtc intervals: There were no significant differences by day across time. Likewise there were no significant differences by time across days. None of the pairwise comparisons was significant.

2.7.4.5 Safety in Special Groups and Situations

2.7.4.5.1 Intrinsic Factors

Body weight and immune status depending on geographic location (high or low transmission area) have been identified to be intrinsic factors.

Body weight:
"Artequin Paediatric Stickpack" is intended for a paediatric population and therefore special emphasis has been put on the analysis of safety information related to this patient group. In study AM-P 001-2005/SPC25-21 a paediatric population with a body weight ranging from 10 to 40 kg has been investigated. This weight range represents very well a paediatric population and the adverse listings presented in section "2.7.4.2.1.1 Common Adverse Events" need no further interpretation.
For the other studies (AM 001-2001 and AM 002-2001) the body weight groups were defined differently and patients with a higher body weight (up to 55 kg) were included. Therefore additional calculations on the incidence of adverse events have been done only including subpopulations with body weight less than 40 kg:

For study AM 001-201 subgroups based on body weight were defined prospectively by the protocol and incidence for adverse events in those subgroups is presented in table 38.

System Organ Class	25-35 kg		36-50 kg		>50 kg		Total	
Treatment group	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
No. of patients	10	10	30	30	62	62	102	102
	No. of AE's in subgroups and (%) of subgroups						No. of AE's in total treatment groups and (%) of treatment groups	
System Organ Class								
Metabolism and nutritional disorders	1 (10)	0	5 (16.7)	6 (20.0)	10 (16.1)	13 (20.9)	16 (15.7)	19 (18.6)
Gastrointestinal disorders	2 (20)	1 (10)	2 (6.7)	1 (3.3)	6 (9.7)	7 (11.3)	10 (9.8)	9 (8.8)
Nervous system disorder	1 (10)	0	0	3 (10.0)	4 (6.4)	6 (9.7)	5 (4.9)	9 (8.8)

Table 38: Analysis of adverse events based on body weight (body weight groups were prospectively defined in the protocol)

Group A: "Simultaneous" treatment with artesunate/mefloquine
Group B. "Sequential" treatment with artesunate/mefloquine

The total number of patients in the subgroups is relatively small and therefore the absolute numbers and percentages must be interpreted with caution. However the incidences of AE's in the low body weight group do not raise any concern that this weight group behaves differently in terms of adverse events as compared to the whole population. For further interpretation see Clinical Overview, sections 2.5.5.4.2 and 2.5.5.4.3.

For study AM 002-2001 the incidence of adverse events has been calculated retrospectively for a body weight group of children with less than 40 kg:

	Body weight ≤ 40 kg		Body weight > 40 kg		Total	
Treatment group	**A**	**B**	**A**	**B**	**A**	**B**
No. of patients	13	17	39	35	52	52
	No. of AE's in subgroups and (%) of subgroups		No. of AE's in subgroups and (%) of subgroups		No. of AE's in total treatment groups and (%) of treatment groups	
System Organ Class						
Gastrointestinal disorders	0	11 (64.7)	9 (23.1)	3 (8.6)	9 (17.3)	14 (26.9)
General disorders	0	2 (11.8)	6 (15.4)	1 (2.9)	6 (11.5)	3 (5.8)
Nervous system disorders	2 (15.4)	1 (5.9)	12 (30.8)	5 (14.3)	14 (26.9)	6 (11.5)

Table 39: Analysis of adverse events for subpopulation based on body weight (both treatment groups) and full treatment groups A and B

Group A: "Simultaneous" treatment with artesunate/mefloquine
Group B. "Sequential" treatment with artesunate/mefloquine

The total number of patient in the subgroup <40 kg is relatively small and therefore the absolute numbers and percentages must be interpreted with caution. However the incidences of AE's in this body weight group do not raise any concern that this weight group behaves differently in terms of adverse events as compared to the whole population. For further interpretation see Clinical Overview, sections 2.5.5.4.2 and 2.5.5.4.3.

Immune status:
In 1998 the WHO published policy guidelines on the use of artesunate and related artemisinin derivatives in combination with mefloquine. Those guidelines made a difference between non-immune and partially immune patients in terms of total dose of mefloquine. However WHO has modified treatment guidelines in the meantime and the immune status is not anymore relevant for dosing of mefloquine.

2.7.4.5.2 Extrinsic Factors

Compliance to malaria therapy concepts is largely dependant on socio-economic status. This issue is discussed in the Clinical Overview, section 2.5.4.2.

2.7.4.5.3 Drug Interactions

Study ART-INT-01-2005 has investigated possible interaction caused by mefloquine on the pharmacokinetics of artesunate/DHA. The pharmacokinetics part of the study has been presented in section 2.7.1 and the safety part of the study has been presented in section 2.7.4 of this document.
The study provides no evidence that mefloquine alters the pharmacokinetic properties of artesunate and its active metabolite DHA. The safety evaluation was limited to the small number (21) of healthy volunteers but does not suggest a safety profile that is different from the safety profile of the single substances.

A possible interaction of artesunate on the metabolism of mefloquine was not investigated within this study program. However this issue is discussed in detail in the "Clinical Overview".

2.7.4.5.4 Use in Pregnancy and Lactation

Pregnant or lactating women were excluded from all studies.

2.7.4.5.5 Overdose

There was no overdosing.

2.7.4.5.6 Drug Abuse

Drug abuse has not been investigated and was not possible because drug intake was done under supervision of study staff.

2.7.4.5.7 Withdrawal and Rebound

No studies were conducted to investigate the effect of withdrawal or rebound.

2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies were conducted to investigate those effects.

2.7.4.6 Postmarketing Data

Artequin Paediatric is on the market in several African malaria endemic countries since June 2006. PSUR's will regularly be prepared.

2.7.4.7 Appendix

Study code	Study title	No. of Subjects entered	Safety population	No. of AE's
1) CS 111	Relative bioavailability of a new tablet formulation of MEPHAQUIN LACTABS® from Mepha Ltd. and LARIAM® from Hoffmann-La Roche Ltd. under fed conditions in healthy volunteers.	40	40	A total of 15 adverse events in 14 subjects were observed during the study. None were rated as serious and 13 were unrelated to treatment. 2 adverse events were probably related to study drug (dizziness and diarrhoea).
2) ART-INT-01-2005	An assessment of the pharmacokinetic interaction between artesunate and mefloquine in healthy Caucasian volunteers.	21	21	No serious adverse events were noted. Adverse events, which were mild, were experienced by about 60% of the volunteers during artesunate and mefloquine dosing (period B) compared with 15% during 3 days of artesunate alone (period A).
3) SPC 25-16	Randomized, single-dose, 3-way cross-over study to investigate the bioequivalence of two dosage forms of artesunate and to investigate the dose proportionality of artesunate pharmacokinetics (Plasmotrim™ Lactab™ oblong).	24	24	No serious adverse events were noted. Nine subjects (37.5%) experienced a total of 21 adverse events (6 moderate and 15 mild adverse events). All subjects recovered without sequelae. For 3 adverse events the relationship to study medication was rated as “probably”, for 6 adverse events the relationship to study medication was rated as “possibly” and for 12 adverse events the relationship to study medication was rated as “not related”.

Table 40: Summary table with AE's recorded from the 3 studies that are not further discussed in the safety section

2.7.5 REFERENCES

No references