

Artequin™ Paediatric Stickpack

Module 2.5. Clinical Overview

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2.5.1 Product Development Rationale

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. Worldwide prevalence of the disease is estimated to be in the order of 300-500 million clinical cases each year and more than 90% of all malaria cases are in sub-Saharan Africa.¹

In fact, out of more than 1 million deaths due to malaria in endemic regions each year, more than 80% occur in Africa south of the Sahara. About 18% of deaths are in children under 5 years of age resulting in one child's death due to malaria every 30 seconds. In addition, an even greater proportion of child deaths is indirectly related to malaria: malaria infections contribute to the development of severe anaemia and make young children more susceptible to severe outcomes of common illnesses such as diarrhoea and respiratory diseases.¹

The great hopes for malaria eradication in the 1960s have failed, and malaria affects now even more people than it did in 1960. One of the major factors that have led to the persistence, and indeed explosion, of malaria disease, despite the availability of very effective antimalarial agents, is the emergence of resistance of *Plasmodium falciparum* to one or more classes of antimalarial drugs. This is due not only to the remarkable adaptability of the parasite, but also to man's own misuse and overuse of drugs for prophylaxis, as well as inadequate treatment of undiagnosed fevers in endemic areas. Chloroquine-resistant *P. falciparum* strains started to appear in the late 1950s and are now common in almost all malarious parts of the world. Moreover, the increase in chloroquine resistant *falciparum* malaria is also driving the cross-resistance to other structurally related quinoline antimalarials.

Treatment of *Plasmodium falciparum* malaria in Africa is increasingly difficult. Resistance to cheap efficient antimalarial drugs poses an increasing threat.² This is especially worrying in West Africa, where many health services depend on chloroquine as the first-line treatment of uncomplicated malaria, despite chloroquine resistance becoming more common. Several African countries have already abandoned chloroquine in favour of sulfadoxine-pyrimethamine (25mg/500mg) because of worsening of chloroquine resistance.³ However, the rapid emergence of resistance to sulfadoxine-pyrimethamine, already seen in East Africa⁴ is growing and is likely to have a striking impact on mortality in many other African regions where no obvious alternatives are available.⁵ Multidrug resistance has rendered most monotherapies for malaria useless in many parts of the world.

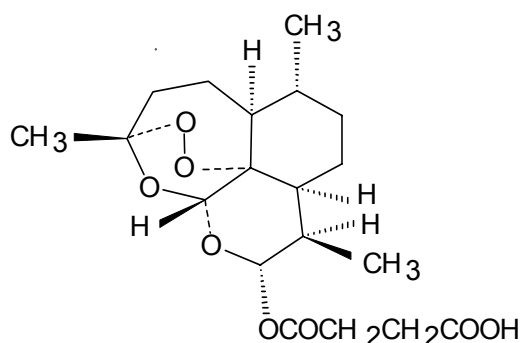
WHO, on the advice of international experts, recommends the introduction of combinations of drugs to replace single drugs in the treatment of *Plasmodium falciparum* malaria. WHO recommends in particular the use of drug combinations containing the peroxidic antimalarial artemisinin (derived from the herb *Artemisia annua*) and its derivatives such as artesunate⁶, i.e., artemisinin-based combination therapies (ACT), which provide an immediate solution to the problem of drug resistance.⁷

These recommendations led to the selection of two highly potent ACT partner drugs, namely artesunate and mefloquine, as active ingredients of Artequin Co-blister tablets as well as the fixed-dose combination (FDC) of Artequin Paediatric Stickpacks, as briefly presented below:

Artesunate:

Artesunate is a water-soluble semisynthetic derivative of the Chinese medicinal herb qinghao (sweet wormwood; *Artemisia annua*). The active antimalarial principle of qinghao, qinghaosu or artemisinin, was isolated and characterized by Chinese scientists in the early 1970s. They confirmed the structure to be a sesquiterpene lactone with a unique endoperoxide bond (a peroxide component), which was shown to be vital for antimalarial activity.^{8,9}

Artesunate is structurally distinct from the other classes of antimalarial agents (see figure 1).



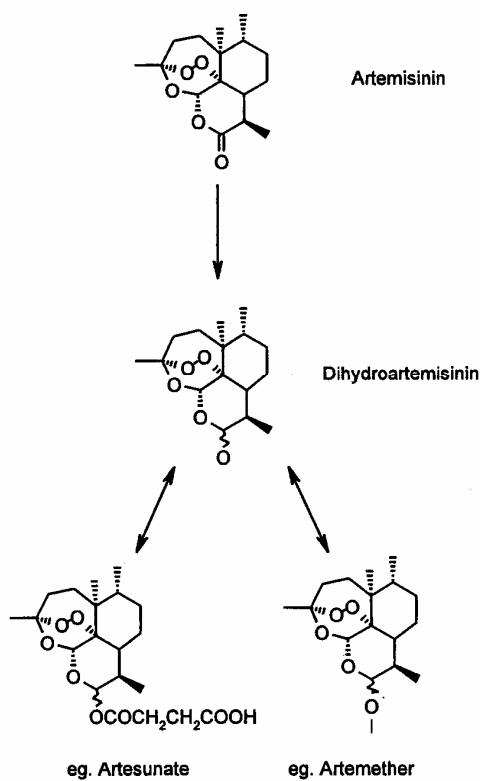


Figure 2 Structure of artemisinin and its derivatives with the common biologically active metabolite dihydroartemisinin¹¹

Artesunate has emerged as suitable component in a combination for a variety of reasons. The artemisinins are the most potent and rapidly acting of the antimalarial drugs, reducing the infecting parasite biomass by roughly 10,000-fold per asexual life cycle, compared to 100 to 1,000-fold for other antimalarials.¹² Second, no stable resistance to this drug class has been reported to date either in clinical isolates or in a laboratory setting.¹³ Reduced susceptibility to artemisinins, however, has already been shown.²⁹ Third, they reduce not only asexual forms but also gametocyte carriage and thus may reduce transmissibility.¹⁴ This is of particular importance, as recrudescence (i.e., resistant) infections are associated with increased gametocyte carriage rates, which provide a powerful selection pressure to the spread of resistance.¹⁵ The fourth advantage is that the artemisinin derivatives are rapidly eliminated and thus provide no opportunity for parasites to be exposed to sub-therapeutic concentrations. Finally, they produce a rapid clinical response, and they have an excellent safety and side effect profile.¹¹

Mefloquine:

Mefloquine was the first synthetic quinoline-methanol compound to be introduced as an antimalarial drug.

Like several other antimalarial drugs, mefloquine is a distant derivative of quinine, as can be seen from the structural formula of mefloquine, quinine and chloroquine. The common feature of all these compounds is the bicyclic conjugated quinoline ring system (figure 3).

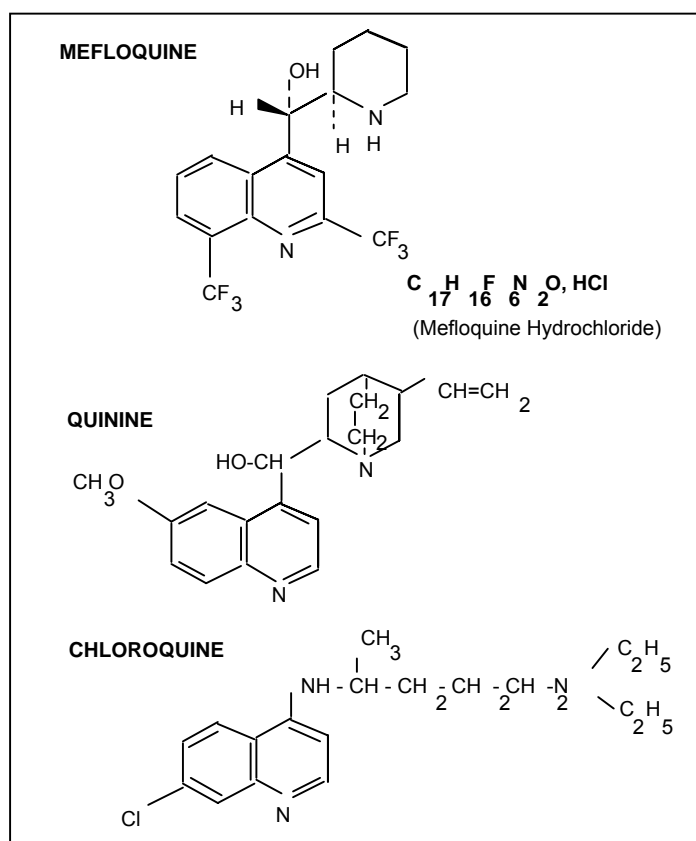


Figure 3 Structural formula of mefloquine, quinine and chloroquine

Mefloquine proved to be effective and safe in the treatment of mild to moderate acute malaria caused by mefloquine-sensitive as well as chloroquine-resistant strains of *P. falciparum*. Cure rates of up to 100 % have been reported in clinical studies in children and adults with mefloquine-sensitive *falciparum* malaria following administration of dosage regimens of mefloquine in monotherapy corresponding to 20-25 mg/kg (for semi-immune patients a reduced dose may be sufficient). Furthermore, the vast accumulation of evidence suggests that mefloquine is a drug with a low incidence of minor adverse effects, and is generally well tolerated although serious adverse effects have been reported rarely.¹⁶

The rationale of adding mefloquine to artesunate is that due to the short half life of artesunate, a certain fraction of parasites may survive (e.g. 0.01% after a single dose,² which then is exposed to long-term (weeks) therapeutic concentrations of mefloquine until complete extinction. Thus, the combination of artesunate with the longer-acting

drug mefloquine, which acts on a different target, supports artesunate in elimination of the remaining parasites thereby improving therapeutic effectiveness, but more importantly, takes over the protecting part of the combination against re-infection with maintained clinically effective mefloquine concentrations for several weeks and thus, might delay or even prevent the emergence of resistance to both mefloquine and artesunate.⁷ In addition, the use of combination therapy has an impact on malaria transmission by lowering rates of gametocytaemia after treatment.¹⁷

There are different ways to combine antimalarial drugs. Compliance with sequential combination regimen is notoriously poor; patients are reluctant to take antimalarials after they feel well. Incomplete treatment leads to poor therapeutic responses and promotes drug resistance. Simultaneous combination of antimalarials not only increases efficacy but also improves compliance by shortening the duration of treatment.

Therefore, in order to limit the development of resistance to both drugs and ameliorate patients' compliance to antimalarial treatments, an optimal simultaneous combination regimen of artesunate and mefloquine in a practical single blister pack has been developed by Mepha Ltd. and successfully tested.^{18,19} Three different solid oral dosage strengths of Artequin (600/1500, 600/750 and 300/750, the numbers indicating the total artesunate/mefloquine dosage per therapy) have been investigated in two randomized, double blind, parallel group, comparative, studies in 308 adults and children with uncomplicated malaria. The results showed that the different Artequin formulations are highly effective and well tolerated in patients with uncomplicated *P. falciparum* malaria. These data have also demonstrated that provision of blister packs of the same daily doses of artesunate and mefloquine is a very effective way to improve compliance with short courses of drug combination, while maintaining comparable therapeutic effect as achieved with sequential regimen commonly used in the past.²⁰

The currently available Artequin dosages were only suitable for children able to swallow tablets and with a body weight of more than 20 kg. However, there was a great need for an Artequin formulation for smaller children unable to swallow tablets.

The new Artequin Paediatric oral formulation presented in this Clinical Overview is a flavoured, taste-masked preparation of pellets of 50 mg artesunate and 125 mg mefloquine as a fixed-dose combination (once daily in one single Stickpack, i.e. 3 Stickpacks for a 3-day treatment of acute uncomplicated *P. falciparum* malaria). It is suitable for children with a body weight of 10 to 20 kg, approximately corresponding to an age between 1 and 6 years.

Based on WHO recommendations,⁷ dosages of artesunate and mefloquine are clearly defined for the given age group. The dosage of Artequin Paediatric follows the official recommendations by the WHO recently adapted also for Africa, i.e., to combine the higher mefloquine dose (i.e., 25 mg/kg total dose over 3 days) with artesunate to prevent development of resistance. With the combination of a total dose of 150 mg artesunate and 375 mg mefloquine, Artequin Paediatric is a dose-linear line extension of the already introduced Co-Blister formulations of **Artequin 300/750** for children (body weight range of >20 to 40 kg) and **Artequin 600/1500** for adults (body weight > 40 kg).

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To fulfil the authorities' requirements for registration of Artequin Paediatric as a line extension of the existing oral dosage forms, a complete pharmaceutical/technical documentation has been prepared. A series of pharmacokinetic studies have been conducted to adduce evidence of the pharmacokinetic characteristics requested for the development of the line-extension (see Section 2.5.2 Overview of Biopharmaceutics). Furthermore, a comparison of the in-vitro dissolution profiles of both the Co-blister tablets and the FDC of Artequin Paediatric had to prove pharmaceutical equivalence of these two different oral formulations, i.e., Artequin 300/750 and Artequin Paediatric Stickpack.

Taking into account the special situation that, for the first time, small African children were offered the new paediatric dosage strength for treatment of malaria, Mepha decided to additionally conduct a confirmatory clinical study to document also therapeutically that administration of the active substances artesunate and mefloquine in the same dose proportionality to small paediatric patients offers a similar efficacy and safety profile as already demonstrated in older children and adults treated with Artequin for *falciparum* malaria.

Therefore, a study has been performed with the objectives to investigate safety and efficacy, as assessed by the 28-day cure rate, of Artequin Paediatric and Artequin 300/750 in a 3-day treatment of children with uncomplicated *Plasmodium falciparum* malaria and to investigate the efficacy parameters in relation to the blood concentration of dihydroartemisinin (DHA) and mefloquine at defined time points. This study will represent an integrated part of this Clinical Overview.

The aim of this document is to review the existing evidence of effectiveness and safety of artesunate used in combination with mefloquine, in the treatment of uncomplicated malaria using different regimen of administration in different endemic regions of the world. Furthermore, the results of the co-administration of artesunate and mefloquine once daily for 3 days (the Artequin concept) will be presented and put into perspective. Efficacy and Safety of studies with the pre-packed blister formulation of Artequin, carried out mainly in Africa will finally be presented to support the evidence of efficacy and safety of Artequin Paediatric described in this Clinical Overview.

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2.5.2 Overview of Biopharmaceutics

To substantiate the final goal of the clinical development of Artequin Paediatric (artesunate 50 mg/mefloquine 125 mg daily for 3 days), 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) and in-vitro investigations have been carried out, namely

- a study on the relative bioavailability of Mephaquin™ Lactabs (the identical galenical composition as for all mefloquine tablets presented in the Co-blister formulation of Artequin) as compared to Lariam® tablets (Study CS 111). Prove of bioequivalence allows to conclude on the similarity to the reference regarding efficacy and safety, and also allow to rely on the whole literature known for Lariam®. The active product ingredient mefloquine from the same source of origin and with identical high quality has also been used as combination partner in Artequin Paediatric.
- a pharmacokinetic interaction study in healthy volunteers to prove lack of impact of mefloquine on the PK characteristics of artesunate when administered together (Study ART-INT 01-2005). The results of this study are highly relevant in demonstrating maintained effective plasma levels during the course of therapy needed for the “Artequin concept” (same dose once daily for three days). This study supports the major importance of the quick but short acting artesunate as the partner of the combination in Artequin Paediatric which has to reduce the parasite load very quickly at the beginning of the therapy.
- a pharmacokinetic study in healthy volunteers to demonstrate the bioequivalence of two oral dosage forms of artesunate (single administration of 50 mg versus 200 mg) and to show the dose proportionality of artesunate pharmacokinetics (Study SPC 25-16). Artesunate tablet formulations identical to those used as 100 mg tablets in Artequin 300/750 and as 200 mg tablets in Artequin 600/1500 have been used. This study supports the concept of down-scaling to Artequin Paediatric (3x50 mg artesunate/3x125 mg mefloquine) from the already existing oral dosage forms (Artequin 300/750 with 3x100 mg artesunate and 3x250 mg mefloquine and Artequin 600/1500 with 3x200 mg artesunate and 6x250 mg mefloquine) in linear proportionality. This dose proportionality is especially important for the quick but short acting artesunate. Due to the dose-linearity known for mefloquine and due to its very long half-life, mefloquine concentration is expected to continuously increase during the three days course of therapy.
- a formal prove of pharmaceutical equivalence of both Artequin Paediatric and Artequin 300/750 presented in this section with the comparison of the in-vitro dissolution profiles, which demonstrate similar release of artesunate and mefloquine from the two oral formulations investigated. As a conclusion, similar release of the active ingredients of Artequin Paediatric and Artequin 300/750 in the gastrointestinal tract, and as a consequence, similar absorption patterns can be expected.

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- a pharmacokinetic investigation to explore the PK characteristics of Artequin administered in the suitable oral forms to children with uncomplicated *P. falciparum* malaria. The results of this study had to support under clinical conditions the relevance of the studies conducted in healthy volunteers as described above and, even more important, to demonstrate that the dose-linearity within Artequin Paediatric and Artequin 300/750 results in similar PK characteristics in their respective target populations, i.e., children with a body weight (BW) of 10 to 20 kg and children with BW of >20 to 40 kg, respectively (PK part of Study AM-P 001-2005).

2.5.2.1 Bioequivalence between mefloquine tablets in Artequin Co-Blister and Lariam® (Study CS 111)

In a 2-way cross-over, open-label, single-dose study the relative bioavailability of mefloquine tablets (Mephaquin™ Lactab™, Mepha Ltd, the mefloquine combination partner in Artequin Co-blister), compared with the standard formulation (Lariam® 250 mg, Hoffmann-La Roche Ltd) was investigated ($n = 40$) (see CS 2.7.1.2.1).

The study design took into consideration the specific PK patterns of mefloquine, namely the long elimination half-life of approx. 20 days. Thus, blood samples were collected during a sufficiently long period of 2016 hours post dose allowing demonstration of the whole elimination phase. After completion of Period I of the study, subjects entered a 9 week washout period prior to crossing over to Period II for administration of the alternative treatment.

The standard bioequivalence analysis showed bioequivalence of mefloquine tablets to Lariam® for both extent and rate of absorption. As demonstration of bioequivalence is generally considered the most appropriate method of substantiating therapeutic equivalence between medicinal products, Lariam® and Mephaquin can be considered as therapeutically equivalent and the same clinical efficacy and safety can be assumed for both products. Mefloquine from the same source of origin with identical high quality has also been used as combination partner in Artequin Paediatric. Since pharmaceutical equivalence between the tablets of the Co-blister formulation and the pellets of Paediatric Stickpacks has been proven (see 2.5.2.4), the same similarity to the reference product Lariam® in terms of efficacy and safety can also be claimed for the mefloquine component of Artequin Paediatric.

2.5.2.2 Pharmacokinetic interaction study with artesunate and mefloquine (Study ART-INT 01-2005)

Although studies have concentrated on the effects of artemisinin derivatives on mefloquine, the investigation of a reverse interaction may be of even greater clinical significance. In these studies described above, only few data have been generated on the pharmacokinetics of the artemisinins. Study ART-INT 01-2005 satisfies the need for

a study in which the possible effects of mefloquine on artesunate/DHA pharmacokinetics are evaluated i) in a crossover design to eliminate between-subject variability, ii) using a regimen which closely parallels that used in clinical practice, and iii) with the confounding effects of recovery from infection eliminated.

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 (see CS 2.7.1.2.2). 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).

There is no evidence from the present study that mefloquine alters the disposition of oral artesunate in healthy male volunteers. The AUC_{0-inf} for the active and rapidly-formed metabolite of artesunate DHA was similar on Period A and B, respectively. Thus, the full therapeutic efficacy of the artesunate daily dose as administered with Artequin Paediatric Stickpacks (i.e., 50 mg artesunate daily over 3 days) can be expected without any influence of mefloquine given concomitantly in the FDC.

2.5.2.3 Bioequivalence and dose proportionality of oral artesunate (Study SPC 25-16)

A mathematical dose-linear up- or downscaling of a galenical formulation is only acceptable if it can be demonstrated that dose proportionality is given in the dose range targeted. For mefloquine a dose linearity can be postulated (plasma levels in micrograms per litre are roughly equivalent to the dose in milligrams administered).²¹ For artesunate, however, dose-linearity is controversially discussed in the literature. Therefore, a study was set up to investigate rate and extent of absorption of artesunate from the given galenical composition (50 mg artesunate tablets as compared to 200 mg artesunate tablets), 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. For this purpose, an open-label, randomized, single dose, 3-way crossover study was carried out on 24 healthy male subjects. The study was conducted in fasting state of the volunteers to avoid confounding effect of food (see CS 2.7.1.2.3).

Based on the DHA PK characteristics regarding the extent and rate of absorption, bioequivalence between the two tablet forms (containing 50mg and 200mg artesunate) could be concluded.

For statistical evaluation of the dose dependency of the pharmacokinetics, dose linearity was investigated by comparing the PK DHA parameters AUC_{0-last} , $AUC_{0-\infty}$ and C_{max} of the administration of 50 mg versus 200 mg artesunate. 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.

Artesunate 50 and 200 mg tablets were chosen for this investigation, since they were the only oral forms of artesunate in identical galenical formulations but different dosage strengths available at the time of the study as Plasmotrim-50 and Plasmotrim-200

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(Mepha Ltd.). With demonstration of the linear dose dependency of the pharmacokinetics, the main prerequisite is provided as a basis for down-scaling the artesunate/mefloquine combination from the already marketed dosage forms of Artequin, namely Artequin 600/1500 and Artequin 300/750 in dose-linear proportionality to Artequin Paediatric (total therapeutic dose: 150 mg artesunate and 375 mg mefloquine). As already stated for mefloquine, it also applies for artesunate that the active substance included as combination partner in both the Co-blister tablet formulations as well as in Artequin Paediatric has the same source of origin and the identical high quality.

Considering the differences in galenical formulations between Artequin Co-blister tablets and the FDC in Artequin Paediatric Stickpacks, a further step in the development program was deemed necessary, i.e., a comparison of the *in-vitro* dissolution profiles as discussed below.

2.5.2.4 Comparison between the dissolution profiles of Artequin Paediatric and Artequin tablets

A formal prove of pharmaceutical equivalence between the pellet formulations of artesunate and mefloquine in Artequin Paediatric and the respective tablet formulations in Artequin 300/750 was essential to permit conclusion of similarity between the two different formulations in terms of efficacy and safety. The *in-vitro* dissolution profiles of the artesunate and mefloquine pellets from Artequin Paediatric Stickpacks were therefore compared with the corresponding tablets of Artequin Co-blister formulations (Artequin 300/375 and 300/750 for children).

In the case of mefloquine, the comparison was performed by calculating the F2 similarity factor of the *in-vitro* dissolution profiles of the mefloquine (125 mg) pellets of Artequin Paediatric (lot G050616, used in Study AM-P 001-2005) with three batches of mefloquine 125 mg tablets (Lots G031010, G031011). Mefloquine 125 has the identical pharmaceutical composition as compared to mefloquine 250 (combination partner of Artequin 300/750, used in Study AM-P 001-2005) in exact dose linearity for both the active substance and the excipients. Pharmacokinetic dose-linearity of mefloquine 125 and 250 mg can be assumed, since PK dose-linearity is proven within the dose range up to 1000 mg mefloquine as described in Section 2.5.3.2.2.

The dissolution was carried out at pH 1.2 as described in the method of analysis. The comparison was carried out by taking values up to 85% mefloquine dissolved (only one at or above that limit) as recommended by the ICH guidelines, which in this instance corresponds to the first 15 min of the dissolution profiles.

Time [min]	Lot. G031010 125 Lactab	Lot. G031011 125 Lactab	Lot. G050616 125 pellets
0	0.00	0.00	0.00
5	46.90	47.64	42.91
10	76.02	75.26	65.19
15	85.96	84.93	78.14
20	90.51	89.28	86.45
25	92.98	91.60	91.67
30	94.35	92.88	94.72

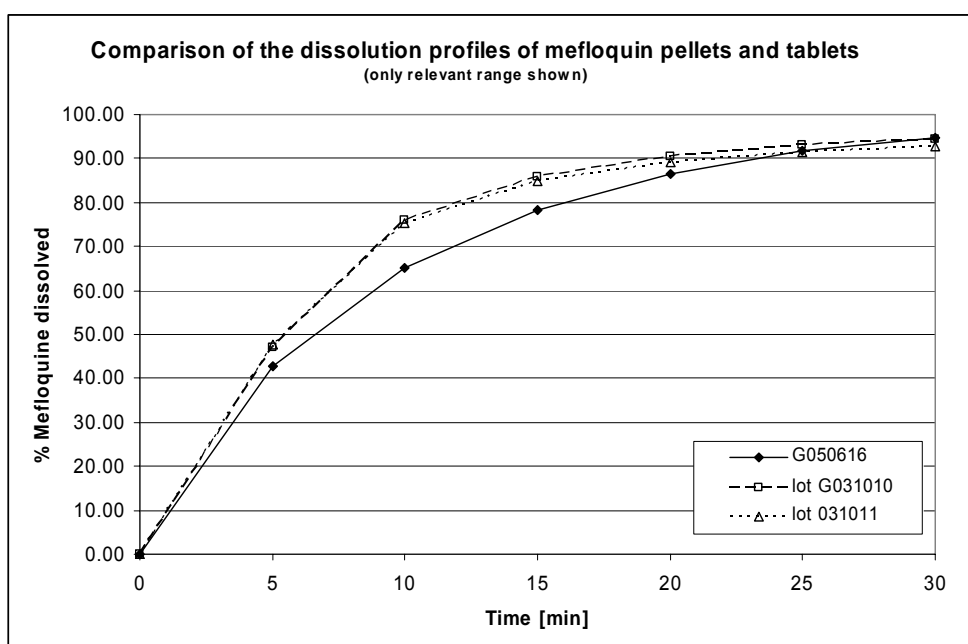


Fig. 7- Dissolution profile of mefloquine pellets and tablets

The below results demonstrate that the similarity factor between the mefloquine pellets in Artequin Paediatric and the mefloquine tablets in Artequin co-blister were very high (acceptance criteria $50 \leq F_2 \leq 100$).

Reference Batch	tested batch	F2 similarity factor
Lot G031010	G050616	58
Lot. G031011	G050616	59

Thus it can be stated that based on the similarity factor the mefloquine pellets in Artequin Paediatric are similar to the mefloquine Lactabs of Artequin and therefore, pharmaceutical equivalence can be concluded.

In the case of artesunate, the comparison was not carried out with the regular pellets present in the Artequin Paediatric Stickpacks but with their uncoated version.

The reason for that choice was as follows:

Since artesunate and mefloquine are bitter, an Eudragit E100 (basic butylated methacrylate copolymer) coat was applied to the pellets rendering them with a neutral taste. Eudragit E100 is slowly dissolving at pH 6.4, the pH of saliva, thus its application as a taste masker, however it is highly soluble at pH 1.2, the pH of the stomach.

In contrast to the use of the coated pellets for the mefloquine similarity test which was calculated using data obtained from dissolution testing carried out at pH 1.2, artesunate being sensitive (unstable) at the referred pH could not be tested at similar conditions. Thus to overcome this hindrance, the test was performed at the conditions described by the analytical method (*i.e.* at pH 7.2) using the pellets before the coating process.

In this instance the above calculation of the F2 similarity factor can not be applied, since it requires at least three data points of which only one can be at or above 85%. As it can be seen from the below table this rule can not be applied. Thus, in such cases dissolution ceases to be a critical parameter. However, a pharmaceutical equivalence between the pellet and the tablet forms of artesunate can equally be concluded based on the high rate of dissolution of both formulations within the first 20 minutes and considering the dissolution profiles of the pellets and tablets which are rather similar as shown with the figure below.

Time [min]	610157 Uncoated pellets	0610627 100mg Tablets	0610634 200mg Tablets
0	0.0	0.0	0.0
10	60.4	74.3	70.8
20	81.3	93.6	95.8
30	91.1	94.1	94.9
40	94.2	92.2	93.6
50	93.1	91.3	92.3
60	91.5	89.4	90.4

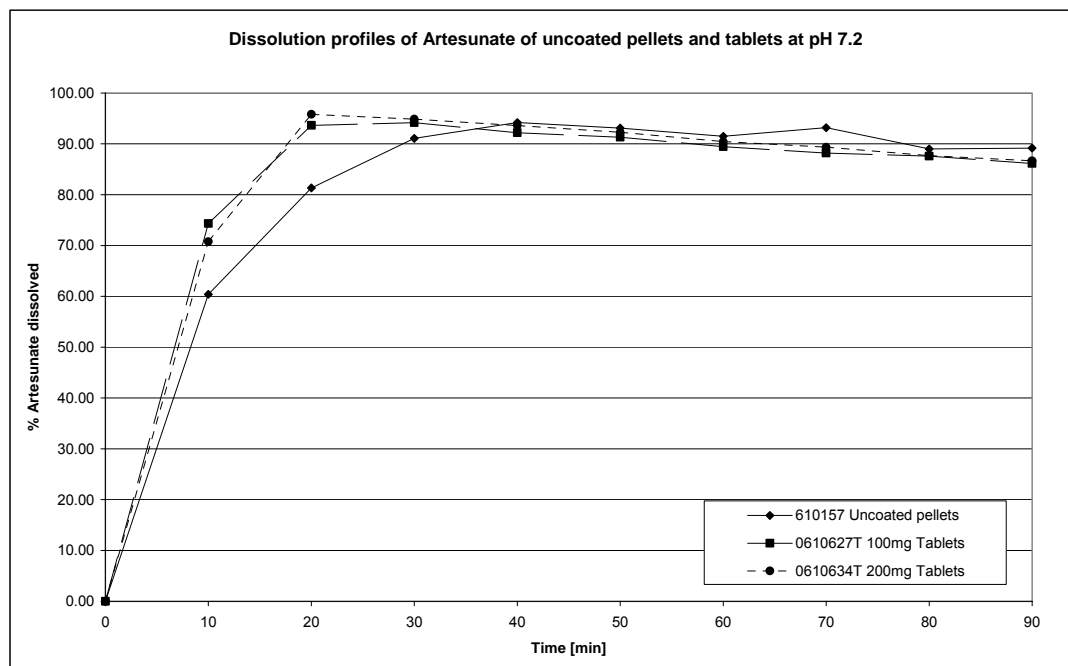


Fig. 8- Dissolution profile of artesunate pellets and tablets

Based on the in-vitro demonstration of pharmaceutical equivalence, similar release of the active ingredients of Artequin Paediatric and Artequin 300/750 in the gastrointestinal tract, and as a consequence, similar absorption patterns can be expected. Therefore, the in-vivo pharmacokinetic and pharmacodynamic characteristics of Artequin Paediatric (pellet formulation of artesunate and mefloquine) can be assumed to be similar to those of Artequin 300/750 (tablet formulation of both active ingredients). This will be confirmed in Study AM-P 001-2005 (see following Section 2.5.2.5).

2.5.2.5 Pharmacokinetic characteristics of Artequin Paediatric and Artequin 300/750 (Study AM-P 001-2005)

A final prove was needed that the galenical dose-linearity realised in the dosage of Artequin Paediatric results in similar PK characteristics in children with a body weight (BW) of 10 to 20 kg as reached with the double dose, i.e., with Artequin 300/750 given to children with BW >20 to 40 kg. This prove was provided in a clinical situation with malaria patients as demonstrated in the PK part of Study AM-P 001-2005 (see CS 2.7.1.2.4).

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 document the remaining blood concentrations at the end of the study period.

This sampling scheme accepted a limitation of the pharmacokinetic assessment of mefloquine due to the fact that the sampling time of 6 hours only comes close to the lower range of t_{max} (8 to 16 hours²¹) 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.

The mean and median plasma DHA concentrations appear very similar between both formulations after administration of each formulation (Artequin Paediatric and Artequin 300/750) to their respective body weight groups. The observed C_{max} values are well above the published in vitro dihydroartemisinin IC50 values for *Plasmodium falciparum* (see Section 2.5.3.2 PK Properties).

Regarding mefloquine, however, in these very small children only a limited number of mefloquine blood samples have been taken (enough to demonstrate the average plasma levels reached at specific time-points but not allowing the formal calculation of PK parameters. 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 slightly 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).

These pharmacokinetic results allow to forecast that appropriate drug plasma concentrations for efficient treatment of *Plasmodium falciparum* infection are reached with both Artequin 300/750 and Artequin Paediatric. It is important to note that the quick but short acting artesunate as the partner of the combination reaches effective blood levels in a short time after administration to reduce the parasite load very quickly at the beginning of the therapy. Within this time the plasma concentration of mefloquine increases to a level expected to be clinically effective supporting artesunate in elimination of the parasites, but more importantly, taking over the protecting part of the combination against re-infection with maintained clinically effective mefloquine concentrations for the 28-days observation period. These results convincingly demonstrate the positive achievement of the Artequin therapy concept successfully adapted by dose-linear down-scaling the Co-blister tablet formulations to the FDC of

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Artequin Paediatric suitable for the patient group of small children with a BW between 10 and 20 kg.

2.5.2.6 Conclusion on Biopharmaceutics

The series of biopharmaceutical and in-vitro studies carried out in the course of development of the Artequin Paediatric Stickpack formulation prove the Artequin concept true also for this FDC of artesunate/mefloquine, namely

- by proving bioequivalence between the mefloquine tablet formulation of Artequin Co-blister and the internationally accepted reference product Lariam® (Study CS 111), both products can be considered as therapeutically equivalent. Thus, the similarity to the reference in terms of efficacy and safety can also be claimed for the mefloquine tablet component of Artequin.
- by demonstrating lack of pharmacological interaction between the two active ingredients artesunate and mefloquine allowing supportive conclusions based on the huge clinical experience with the single substances (ART-INT 01.2005). Thus, the full therapeutic efficacy of the artesunate daily dose of 50 mg as administered with Artequin Paediatric Stickpacks can be expected without any influence of mefloquine given concomitantly in the FDC.
- by proving dose linearity and proportionality for artesunate in the dose range of 50 to 200 mg as used in the range of Artequin preparations. With demonstration of the linear dose dependency of the pharmacokinetics, the main prerequisite is provided as a basis for down-scaling the artesunate/mefloquine combination from the already marketed dosage forms of Artequin 600/1500 and 300/750 in dose-linear proportionality to Artequin Paediatric with a total therapeutic dose of 150 mg artesunate and 275 mg mefloquine (Study SPC 25-16).
- to prove similarity between the dissolution profiles of the artesunate as well as mefloquine pellets in Artequin Paediatric and of the artesunate and mefloquine tablets in Artequin co-blister and, thus, to conclude on pharmaceutical equivalence. Based on these in-vitro results similar release of the active ingredients of Artequin Paediatric and Artequin 300/750 in the gastrointestinal tract, and as a consequence, similar absorption patterns can be expected resulting in similar pharmacokinetic and pharmacodynamic characteristics of both the Artequin Co-blister tablet forms of artesunate and mefloquine and the FDC pellet formulation of both active ingredients in Artequin Paediatric Stickpacks.
- to finally prove that the galenical dose-linearity realised in the dosage of Artequin Paediatric results in similar PK characteristics in children with a body weight (BW) of 10 to 20 kg as reached with the double dose, i.e., with Artequin 300/750 given to children with BW >20 to 40 kg. This prove was provided in a clinical situation with malaria patients as demonstrated in the PK part of Study AM-P 001-2005.

Overall, the results discussed in this Section convincingly demonstrate the successful adaptation of the Artequin therapy concept by dose-linear down-scaling the Co-blister tablet formulations to the FDC of Artequin Paediatric. Artequin Paediatric is a well

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defined dose-linear line extension of Artequin 300/750 for children (body weight range of >20 to 40 kg) and Artequin 600/1500 for adults. Clinically even more important, the pharmaceutical equivalence is confirmed by similar PK characteristics demonstrated in study AM-P 001-2005.

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2.5.3 Overview of Clinical Pharmacology

2.5.3.1 Pharmacodynamic Activity of Oral Artesunate and Mefloquine

2.5.3.1.1 Pharmacodynamics of Artesunate

The sesquiterpene lactone ring of artesunate with the unique endoperoxide bridge appears to be vital for the antimalarial activity of the drug. The following mechanism of antimalarial action has been described:

Early work suggested that artesunate acts via a two-step mechanism.²²

1. intra-parasitic haem-derived iron catalyzes the cleavage of the endoperoxide bridge into hydroperoxide.
2. The resultant hydroperoxide-metal complex is a powerful oxidising agent, believed to release free radicals which then kill the parasite by alkylating and poisoning one or more essential parasite proteins and haem.

Other processes which were supposed to play a role in the antimalarial effect of artesunate are the preferential inhibition of plasmodial DNA synthesis, and the dose-dependent inhibition of the activity of cytochrome oxydase, an enzyme located in the plasmodial plasma membrane, nuclear membrane and limiting membrane of food vacuole.²³ All these processes take place in the very early phase of erythrocytic schizogony, i.e., in the early stages of asexual development of the parasite in the blood.

Investigations on artemisinin mode of action are still going on driven by the fear of development of resistance to this class of antimalarial drugs. The main goal of these investigations is to deploy artemisinin as combination partners for multidrug resistant malaria.²⁴

Looking at pharmacodynamic activity against the parasite *in vitro*, a number of experiments in *P. falciparum* have shown that artemisinin derivatives are active against a broad spectrum of the life cycle of the parasite (from the relatively metabolically inactive ring stages to late schizonts). They have also been shown to prevent cytoadherence *in vitro*, probably by preventing development to the mature trophozoite stage.¹¹

Artemisinin derivatives, including artesunate, appeared to prevent gametocytogenesis in patients with falciparum malaria.¹⁰ A study in Gambian children with acute *P. falciparum* malaria¹⁴ demonstrates the gametocidal efficacy of artesunate during the long period (8 to 10 days) of gametocyte development and maturation. The results showed a significantly lower gametocyte prevalence and density following treatment with artesunate combinations which support the conclusion that there is an effect of

artesunate on sexual stages of the parasite. Artesunate might therefore reduce or prevent transmission of the disease. Furthermore, artesunate affected the transmission of the disease by reducing post-treatment infectivity but without abolishing it completely.¹⁴

2.5.3.1.2 Pharmacodynamics of Mefloquine

The mechanism of antimalarial action of mefloquine is reasonably defined. Mefloquine, like chloroquine and quinine, is a blood schizonticidal agent and is active against the intraerythrocytic stages of parasite development. It has a high affinity to erythrocyte membrane, where it preferentially binds with phospholipids, and may thus possibly block the invasion of uninfected erythrocytes by merozoites.²⁵ The concentration of mefloquine in infected red blood cells is higher than that in non-infected ones, mainly due to accumulation by binding with ferriprotoporphyrin IX (hematin) which is formed in the course of haemoglobin degradation by plasmodia. The mefloquine-hematin complex is toxic for the malaria parasite and is believed to interfere with protease and peptidase activity in the acid environment of the parasite's food vacuoles.²⁵

Mefloquine has efficacy against the late trophozoite stage of all species of human malaria parasite but, like most antimalarial drugs other than the artemisinins, probably has little activity against circulating (ring forms) of *Plasmodium falciparum*. Mefloquine is ineffective against the hypnozoite stages of *P. vivax* and *P. ovale* which, although not pathogenic, persist in the liver and may cause late relapse. Treatment of *P. vivax* malaria with mefloquine must therefore be followed by a course of primaquine for eradication. *P. falciparum*, the agent of the severest clinical forms of malaria, does not have a hypnozoite stage.²⁶

Mefloquine is a non-competitive inhibitor of acetylcholinesterase and butyrylcholinesterase. This may account for side effects involving the gastrointestinal system (e.g., nausea and vomiting) as well as the CNS (e.g., hallucinations and disorientation) observed at relatively high drug concentrations.²⁵

2.5.3.1.3 In vitro Investigations of Artesunate and Mefloquine

The synergistic and additive effect of artesunate with other antimalarial drugs were tested *in vitro* in chloroquine and mefloquine-sensitive and -resistant strains of *P. falciparum*. The preliminary findings have shown that artesunate and mefloquine have an additive inhibitory effect against mefloquine-sensitive and -resistant *P. falciparum* isolated from Thai patients,¹⁰ and a synergistic inhibitory effect against chloroquine-sensitive and -resistant strains.²⁷

Nowadays, it is generally accepted that additivity and synergism with artesunate and mefloquine increase the clinical usefulness of either drug, and is of value in delaying the emergence of resistance to either drug.^{28,29} Based on these considerations, the WHO officially recommends the concept of artemisinin-based combination therapies (ACTs) for treatment of uncomplicated multi-drug resistant *falciparum* malaria.

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2.5.3.1.4 Development of Resistance

Plasmodial resistance to some antimalarial drugs is thought to develop as a result of spontaneous chromosomal point mutation, which occurs independently of drug pressure.

Subsequently, more resistant mutants are selected under drug pressure. Resistant parasites are most likely to be selected if the heterogeneous parasite population is exposed to sub-therapeutic concentration of drug, and the resistant parasites survive to produce gametocytes that are then transmitted to other individuals by the mosquito vector.

The development of cross-resistance or reduced sensitivity to antimalarial drugs with differing mechanism of actions, such as artemisinin, chloroquine, quinine and mefloquine, suggests that resistance is mediated via membrane changes which prevent the drugs from reaching their different intracellular sites of action.

Artesunate:

In vitro experiments have demonstrated that chloroquine-resistant and chloroquine-sensitive strains of *P. falciparum* are equally sensitive to artesunate.³⁰ Therefore, it is unlikely that there is any cross-resistance between artesunate and chloroquine.

It appears relatively difficult to induce resistance to artesunate in experimental conditions. Even after 130 days of stepwise discontinuous exposure of isolates of *P. falciparum* to artesunate, the plasmodia remained extremely drug sensitive.¹⁰

By using the index of resistance which is determined by dividing the dose required to suppress parasitaemia on day 4 by 90 % (ED₉₀) for infections caused by resistant strains by the ED₉₀ for infections caused by sensitive pathogens, it was shown that the artesunate index of resistance was 1.28, indicating little development of resistance to this drug.¹⁰

Further *in vitro* studies revealed no increase in artesunate IC₅₀ values for multidrug-resistant *P. falciparum* isolated from Thai patients experiencing recrudescence of disease after artesunate monotherapy compared with pre-treatment values.³¹ Artemisinins are in fact unique among antimalarials in that there is still no evidence of significant resistance in clinical isolates.²⁴ There are, however, some reports on decreasing in-vitro sensitivity of *P. falciparum* to artemisinin derivatives mainly found in regions like China where artemisinins were deployed for more than a decade on a large scale as monotherapy. Decreasing drug efficacy shown in isolated cases in Asia is a first warning sign for the risk of resistance development, especially following poor treatment regimen (too short duration of monotherapy with often substandard quality of drugs). Therefore, WHO strongly recommend to replace oral artemisinin monotherapies by high quality ACTs to prevent development and spread of resistance to artemisinin derivatives.²⁹

Mefloquine:

Resistance to mefloquine remains limited to certain area of South-East Asia. Nevertheless, there is increasing concern about the widespread of resistant *P. falciparum*.

It has been shown that the basis of resistance may be the amplification of certain genes which enable the parasites to pump the antimalarial drug out of the cell. Two multi-drug resistant genes (pfmdr1 and pfmdr2) have been identified for *P. falciparum*. Mutations in pfmdr1 can confer resistance to mefloquine, quinine and halofantrine.³² Resistance to mefloquine appears to be distinct from chloroquine resistance, as shown by the activity of mefloquine against chloroquine resistant *P. falciparum*.

Antimalarial drugs susceptibility of fresh isolates of *P. falciparum* from patients who have been treated with the combination of artesunate (4 mg/kg/day for 3 days) and mefloquine (25 mg/kg) between 1995 and 1999 have been tested in Thailand.³³ The results have shown that despite intensive use of this combination during 4 years, there has been a significant improvement in mefloquine sensitivity ($p < 0.001$) and artesunate sensitivity ($p < 0.001$) *in vitro*. These observations support the *in vivo* findings that the combination of artesunate and mefloquine has reversed the previous decline in mefloquine sensitivity.¹⁷ In successfully treated patients, mefloquine also protects artesunate by removing all residual parasites originally exposed to the artemisinin derivative. Thus, there is no pressure to develop artesunate resistance even if the combination is broadly used.

This findings were path breaking and assigned the strong advance and extension of the ACT concept, first in Asia, later on followed by the other endemic regions of the world.

Artesunate combined with Mefloquine

Artesunate and mefloquine are both schizonticidal but destroy by different modes of action the erythrocytic asexual forms of the causative agents of malaria in humans (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*).^{22,24,25} These properties in combination with different elimination half-life render them ideal as combination partners for an ACT, i.e.,

- Different modes of action to protect each other drug against development of resistance
- quick but short acting artesunate to reduce the parasite load very quickly at the beginning of the therapy
- long acting mefloquine to partially support artesunate in elimination of the parasites, but more importantly, taking over the protecting part of the combination against re-infection

The combination of artesunate and mefloquine is usually also effective against malaria pathogens that have developed resistance to other antimalarial agents such as chloroquine, proguanil, pyrimethamine as well as sulfadoxine-pyrimethamine combinations.

Artequin with it's new concept of therapy (once daily the same dose given over three days) takes advantage of additivity and synergism of artesunate and mefloquine to

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associate these antimalarials to an advantageous ACT fulfilling the recommendations of the WHO. The dose range of the Co-blister tablet formulations of Artequin 600/1500 and Artequin 300/750 has now been completed by the FCD of Artequin Paediatric Stickpacks. Thus, the whole dosage range of Artequin can now be used for patients over the whole range of body weight from adults down to small children with a body weight above 10 kg. The outstanding pharmacodynamic properties of the combination artesunate/mefloquine, e.g., additivity and synergism leading to improved efficacy in uncomplicated *P. falciparum* malaria and protection of either antimalarials against development of resistance, can also be exploited in the group of small children between 10 to 20 kg of body weight urgently reliant on an effective antimalarial therapy in a galenical form especially developed and suitable for them.

2.5.3.2 Pharmacokinetic Properties of Oral Artesunate and Mefloquine

PK characteristics of the two antimalarials artesunate and mefloquine administered alone will first be presented as derived from the literature. Since there is no relevant pharmacokinetic interaction to be expected in case both antimalarials are administered together as discussed in Section 2.5.2.2, kinetics of the monosubstances may also apply to the combination, Nevertheless, the informations derived from the literature will be put in relation to the outcome of PK investigations carried out with Artequin in paediatric populations, namely with the Co-blister tablet formulations of Artequin 300/750 and the FDC in Artequin Paediatric Stickpacks.

2.5.3.2.1 Pharmacokinetics of Artesunate

Following isolation of artemisinin in the 1970s, various techniques for an analytical assay of the drug and its derivatives have been studied. The high performance liquid chromatography with electrochemical detection (HPLC-ECD) technique has become the method of choice for the specific measurement of artemisinin and its derivatives in biological fluids. This method is sensitive and specific, thus allowing quantification of the parent drug and the most important metabolite, dihydroartemisinin (DHA), at levels approaching 5 ng/ml.³⁴ In addition, a bioassay is available that measures the combined activities of both parent compound and metabolite in plasma.³⁵

Nevertheless, interpretation of the plasma concentration/time profile for artesunate is complex, firstly because the compound binds tightly to erythrocyte membranes¹⁰ and secondly the orally administered drug is rapidly hydrolyzed to the principal active metabolite dihydroartemisinin (DHA) and thus, only appears in the blood transiently in concentrations that are detectable by current assay techniques. Therefore, studies investigating the pharmacokinetic characteristics of artesunate mainly rely on the plasma concentrations of it's active metabolite, DHA.

The absorption, distribution, metabolism and elimination characteristics of oral artesunate can be summarized as follows:

Absorption:

Following oral administration, artesunate is quickly absorbed and reaches a maximum plasma concentration (C_{max}) on average between 0.5 and 1 hour.³⁵

Distribution:

Artemisinin and its derivatives accumulate selectively in parasitised red blood cells through binding to yet unidentified receptor(s). The concentration of DHA in *P. falciparum*-infected erythrocytes *in vitro* was found to be 300-fold the plasma concentration (compared to less than 2-fold for uninfected erythrocytes). This is probably due to the altered membrane structure of infected erythrocytes.³⁵

Artesunate and DHA bind modestly to human plasma protein. The degree was found to be about 59 % for artesunate and 43 % for DHA.³⁵

Metabolism:

In vivo, artesunate is hydrolysed rapidly by blood esterases and the hepatic cytochrome P450 system, to dihydroartemisinin (DHA), which is also highly effective against malaria.³⁶

Elimination:

The mean elimination half-life of artesunate is approximately 0.5 hours. The active metabolite, DHA has a mean elimination half-life of 0.75 hours and is eliminated slower than the parent compound. DHA is cleared predominantly by hepatic biotransformation to pharmacologically inactive metabolites.

Pharmacokinetics in special clinical situations

There have been no specific pharmacokinetic studies with artesunate in patients suffering from *renal insufficiency*, however, only a small fraction of this drug is eliminated via the kidneys.

It has been shown that *hepatic insufficiency* has no effect on the bioavailability and clearance of oral artemisinin.³⁵ However, no specific data is available on the use of artesunate in this patient population.

Food effects:

No data on artesunate are available but it seems that food intake does not affect the pharmacokinetic parameters of artemisinin.³⁵

Drug interactions:

The synergistic effect of artesunate combined with other antimalarials like mefloquine to improve efficacy and to prevent either drug from the development of resistance is generally exploited in the ACT concept as previously discussed in Section 2.5.3.1.4. No clinically relevant pharmacokinetic interaction between artesunate and mefloquine could be demonstrated (see also Section 2.5.2.2).

No clinically relevant drug-drug interactions between artesunate and other drugs have been reported so far.

2.5.3.2.2 Pharmacokinetics of Mefloquine

The pharmacokinetic properties of mefloquine have been extensively reviewed by Karbwang and White³⁷ as well as by Palmer et al.³⁸

The mefloquine absorption, distribution, metabolism and elimination characteristics can be summarized as follows:

Absorption:

Maximal plasma concentrations of mefloquine are attained 6 to 24 hours (mean about 17 hours) after a single oral dose.

In volunteers, maximum plasma concentrations in $\mu\text{g/l}$ are roughly equivalent to the dose in milligrams. For example, at a dose of 1000 mg of mefloquine, plasma concentrations (C_{max}) of about 1000 $\mu\text{g/l}$ can be measured, demonstrating a pharmacokinetic dose-linearity in this dose range. After taking 250 mg (1 Lactab) per week steady state maxima of 1000-2000 $\mu\text{g/l}$ have been found after 7-10 weeks.²¹

Distribution:

Depending on the parasitemic state and the duration of the infection, the concentration of mefloquine in the erythrocytes amounts to almost two to fourfold the plasma concentration.

The distribution volume varies between 16 and 25 l/kg. More than 98% of the active ingredient is bound to plasma proteins. Mefloquine crosses the placental barrier and reaches breast milk in apparently minimal amounts.

Metabolism:

Several metabolites of mefloquine have been identified. The principal metabolite of mefloquine is the corresponding quinoline carboxylic acid, which is inactive against *P. falciparum*. In healthy volunteers the carboxylic acid metabolite could be detected in the plasma 2-4 hours after a single oral dose. Maximal plasma concentrations, which were 50% higher than those of mefloquine, were attained after two weeks. Subsequently the plasma levels of both, the principal metabolite as well as mefloquine, fell at approximately the same rate. The area under the plasma concentration curve

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(AUC) for the principal metabolite was 3-5 times larger than that for the parent substance. The other metabolite, an alcohol, was present only in very small amounts.

Elimination:

The calculated mean elimination half-life of mefloquine is 21 days (15-33 days). Total clearance, which occurs mainly in the liver, is in the range of 30 ml/min. There is evidence that mefloquine is excreted principally in the bile and the feces. In volunteers the excretion of unchanged mefloquine and its principal metabolite in the urine reached 9% and 4%, respectively, of the administered dose. It was not possible to determine the concentrations of other metabolites in the urine.

Pharmacokinetics in special clinical situations:

There have been no specific pharmacokinetic studies with mefloquine in patients suffering from *renal insufficiency*, however, only a small fraction of this drug is eliminated via the kidneys. It should be noted that mefloquine and its principal metabolite are not removed to an appreciable extent by haemodialysis.

The elimination of mefloquine in patients with *hepatic insufficiency* may be delayed, which leads to higher plasma concentrations.

The pharmacokinetics of mefloquine may be modified in *acute malaria*.

Pharmacokinetic differences regarding mefloquine have been observed between various *ethnic populations*. In practice however, these are of minor importance compared to the immune status of the host and the sensitivity of the parasite.

Food effects:

The presence of food in the stomach increases the rate and extent of absorption in healthy volunteers considerably and leads to an increase in bioavailability by approximately 40%.³⁹ This fact is important in prophylactic use of mefloquine in healthy travellers where effective prophylactic levels should be reached before departure to the endemic region, in general after two weekly doses of mefloquine. The possible influence of food intake on bioavailability during a short-term therapy with mefloquine may play a minor role. In patients suffering from malaria, food intake is often limited at the start of therapy by the symptoms of the disease itself. Regarding bioavailability of mefloquine in the 3 days concept of combination it is more important to note, that bioavailability is considerably increased with the recovery from the disease already when the second oral dose is given.⁴⁰ Furthermore, capacity limited absorption of mefloquine in malaria if given in one single dose or two doses the same day is compensated by the total dose split to three equal daily doses as used in the Artequin concept.⁴¹

Drug interactions:

Concomitant administration of mefloquine and related substances (e.g. quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions. Therefore, halofantrine, which is known to cause QT interval prolongation, must not be administered concomitantly with or after mefloquine for at least 3 weeks. In patients undergoing treatment with anticonvulsives such as valproic acid, carbamazepine, phenobarbital or phenytoin, mefloquine may lower the plasma concentration of the anticonvulsive, resulting in seizures. In such cases, it may be required to adjust the dosage of the anticonvulsive.

2.5.3.2.3 Pharmacokinetic properties of the combination artesunate/mefloquine

Mefloquine has no effect on plasma concentration profiles of oral artesunate (see Study ART-INT 001-2005). There are other similar data after the administration of DHA supporting the conclusion that mefloquine does not influence the absorption, distribution, metabolism or excretion of artesunate.

From the available literature, artesunate (or DHA) is unlikely to have significant impact on the absorption and distribution of mefloquine. Some observations on C_{max} values made by Karbwang et al.⁴² could mean that artesunate reduces the bioavailability of mefloquine. Data from other studies do not support this conclusion, but rather suggest that artesunate and mefloquine can be given together with confidence.⁴³

Regarding metabolism and excretion, available evidence suggests that the terminal elimination half-times for these drugs are similar whether they are given alone and in combination.⁴³ Furthermore, *in vitro* studies have shown that artesunate does not alter mefloquine metabolism by human liver microsomes.⁴⁴

As a consequence, PK characteristics of both artesunate and mefloquine are basically identical when administered alone or in combination. Therefore, the special clinical properties of the two antimalarials (fast but short acting artesunate – long lasting additive and protective effect of mefloquine) which are important for the ACT concept as used in Artequin Co-blister and the FDC Artequin Paediatric, are fully maintained in the combination.

2.5.3.2.4 Pharmacokinetics of Artequin in paediatric patients as compared to published data in the literature

In the PK part of Study AM-P 001-2005, the DHA and mefloquine concentrations in plasma were reported at time points specified for each individual for each of the two paediatric treatment groups separately (see also 2.5.2 Overview Biopharmaceutics and CS...). In spite of the similarity in dissolution profiles demonstrated *in-vitro*, no formal bioequivalence calculation was planned in this study between the two investigational drugs. Nevertheless, descriptive statistics were applied to demonstrate clinically relevant similarities in pharmacokinetic properties between Artequin 300/750 (Co-blister tablet formulations) and Artequin Paediatric (FDC pellet formulations) as shown below.

Dihydroartemisinin

The PK characteristics found in the two paediatric groups investigated appear very similar between both formulations (A: Artequin Paediatric in children with 10 to 20 kg of body-weight, B: Artequin 300/750 in children with a body-weight between >20 and 40 kg). The longer $t_{1/2}$ after formulation B (1.85 vs 1.06 hours) may clinically not be relevant and is likely due to the presence of an outlier ($t_{1/2}$ reached after 10.1 hours) that influenced disproportionately the mean value.

The observed mean C_{max} values were 1181 (Group A) and 1080 ng/ml (Group B) and are, therefore, well above the published *in vitro* dihydroartemisinin IC50 values for *Plasmodium falciparum* [median and range 1.22(0.14–6.60) ng/ml, geometric mean and range 0.32(0.07–1.30) ng/ml] reported by Ringwald, Bickii and Basco⁴⁵. A mean C_{max} of 1137 ng/ml was reported by Binh⁴⁶ with a dose equivalent to 120 mg artesunate, C_{max} values similar to those shown in the Artequin study discussed.

The observed $t_{1/2}$ values as described above are slightly longer than those reported in Vietnamese adult patients with *falciparum* malaria⁴⁶ receiving 120 mg of oral artesunate who had a mean $t_{1/2}$ of 0.88 hours. However, the shorter sampling schedule (ending at 4 hours after dosing) in this study might be the explanation. Available pediatric results⁴⁷ were obtained after a 3 mg/kg dose (as compared to 2.5–5 mg/kg daily dose in the present Artequin study). Results have to be viewed with caution as a bioassay was used to determine artesunate concentrations – due to this reason, this article will not be used in this discussion to compare C_{max} or AUC values. Using “model-independent” methodology based on polyexponential curve stripping that is in practice equivalent to compartmental modelling, a mean $t_{1/2}$ of 1.0 hours was demonstrated, a broadly similar value to those obtained in the two paediatric groups treated with Artequin.

The t_{max} was similar with a median of 1.58 hours in the patients receiving oral artesunate reported by Binh et al.⁴⁶ Bethell et al.⁴⁷ report a mean value of 1.7 hours.

Regarding $AUC_{(0-inf)}$, the mean (95% CI) values in the study reported by Binh et al.⁴⁶ were 2189.88 (1450.44–2929.32) h*ng/ml. These values are somewhat lower than those in the current study (Group A: 3157, Group B: 3243 h*ng/ml), probably due to the shorter $t_{1/2}$, thus the same caveat about the different sampling schedules applies.

Mefloquine

As explained in Section 2.5.2 Overview Biopharmaceutics, for ethical reasons in these very small children of study AM-P 001-2005 only a limited number of mefloquine blood samples have been taken (enough to demonstrate the average plasma levels reached at specific time-points but not allowing the formal calculation of PK parameters). The mean mefloquine plasma concentrations 6 hours after the administration of the first dose of Artequin 300/750 or Artequin Paediatric to their 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 (group B) given to children weighing 20–40 kg. Values at the end of the observation period of 28 days are, however, higher in this group with a (mean(SD) of 337.33(117.58) ng/ml as compared to 239.23(132.8) ng/ml in group A). Thus, with the sparse sampling schedule defined for mefloquine, the

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C_{max} values have clearly been missed. It is, nevertheless, important to demonstrate, that 6 hours after dosing, i.e., at the time when the DHA concentrations decrease towards zero, maximum observed mefloquine concentrations reach clinically relevant and effective values as demonstrated in the comparison with published data of different studies shown below.

In the present study, the observed median mefloquine concentrations 6 hours after dosing on day 3, i.e., the sampling point where the highest concentrations were measured, were 2550 ng/ml in group A patients and 1815 ng/ml in group B patients.

Median mefloquine C_{max} in the report by Na-Bangchang et al.⁴⁴ ranges from 2310 to 3460 ng/ml depending in the formulation, and mean±SD values in the mefloquine + artesunate group in the Karbwang et al. report (29) are 1623±388 ng/ml. Therefore the values reported in the literature for mefloquine C_{max} in adults are similar to the observed maximum mefloquine concentrations in study AM-P 001-2005. As a possible approximation, given the limitations of the sampling schedule in this study, actual C_{max} values would be expected not to differ too much from those in the Thai adults reported in the Na-Banchang et al.⁴⁴ and Karbwang et al.⁴² articles.

Regarding pediatric data, Price et al.⁴⁸ report median(range) whole blood C_{max} values after 4 mg/kg of artesunate given for 3 days with 15 mg/kg of mefloquine given on days 2 and 3 – the closest conditions to this study – of 1377 (838-3106) ng/ml. These values are somewhat lower than those in the Artequin paediatric study. Comparison is however difficult as they gave 25 mg/kg mefloquine as single dose or in split doses (15 and 10 mg/kg on days 2 and 3, respectively) rather than the 6.25-12.5 mg/kg mefloquine doses given in days 1 to 3 in the Artequin paediatric study. A different but also relatively sparse sampling schedule and the timing they used (one sample per day) render it also unlikely to actually obtain samples near t_{max} .⁴⁸

The mean(range) mefloquine concentrations measured at day 28 were 239.23(99.7-518.0) ng/ml for group A and 337.33(156.0-544.0) for group B. Prior results⁴⁹ after 4 mg/kg of artesunate and simultaneous mefloquine 15 mg/kg given simultaneously to Vietnamese patients 6 years or older with symptomatic, non-severe *falciparum* malaria showed geometric mean(range) concentrations after 28 days of 316(119-963) ng/ml, i.e. similar to the Artequin paediatric study results in group B, although values in group A appear somewhat lower.

The maximum observed mefloquine concentrations in the Artequin study are clearly higher than the reported *in vitro* IC50 values reported in Gabonese isolates⁵⁰ of 4.69 ng/ml in the Franceville area and 9.27 ng/ml in the Bakoumba area.⁵¹ Even the minimum observed values in the Artequin study exceed 800 ng/ml and the reported values are likely to be below this value. Due to the long $t_{1/2}$ of the drug, and the presence of concentrations over these IC50 values in the 28 day sample, duration of inhibitory mefloquine concentrations are appropriate. Furthermore, Phillipps et al.⁵² report results using as the measure of susceptibility EC50 rather than IC50, that are of special interest as they come from one of the study centres (Lambaréné Hospital). They report a mean(95% CI) EC50 for mefloquine against *Plasmodium falciparum* clinical isolates of 192.93(162.67-230.76) ng/ml, well below the 28-day mefloquine concentrations reached with either therapy in the Artequin paediatric study.

Comparison of the PK results of study AM-P 001-2005 with the relevant literature data clearly demonstrate that both paediatric dosage forms of Artequin, i.e., Artequin

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Paediatric and Artequin 300/750, with a mean total therapeutic dose of 12 mg/kg artesunate and 25 mg/kg mefloquine each, reach similar plasma profiles in both paediatric populations (10 to 20 and >20 to 40 kg body-weight) in a concentration range adequate to achieve the high clinical efficacy expected for this ACT concept of artesunate/mefloquine. Thus, also from a pharmacokinetic point of view, the FDC Artequin Paediatric Stickpack can be accepted as a real line extension of the Co-blister tablet formulations of Artequin as demonstrated by the comparison with the PK properties of Artequin 300/750.

2.5.4 Overview of Efficacy

Acute malaria is characterized by fever and associated clinical phenomena including tachycardia, tachypnoea, headache, muscle pains, abdominal pain, nausea, vomiting, diarrhoea, delirium and orthostatic hypertension.

The clinical manifestations of the disease are dependent on both the species of the infecting *Plasmodium* and the immunological status of the patient. Malaria caused by *P. falciparum* is the most severe form of the disease and may be complicated by cerebral malaria, acute renal failure, hypoglycaemia, pulmonary oedema, massive haemolysis, severe normocytic anaemia and acidaemia or acidosis.⁵³

Because of the possibility of severe complications, *P. falciparum* constitutes a medical emergency, and appropriate treatment should be initiated as soon as possible. The primary aims of the treatment are to prevent death and alleviate the symptoms of the disease as rapidly as possible.

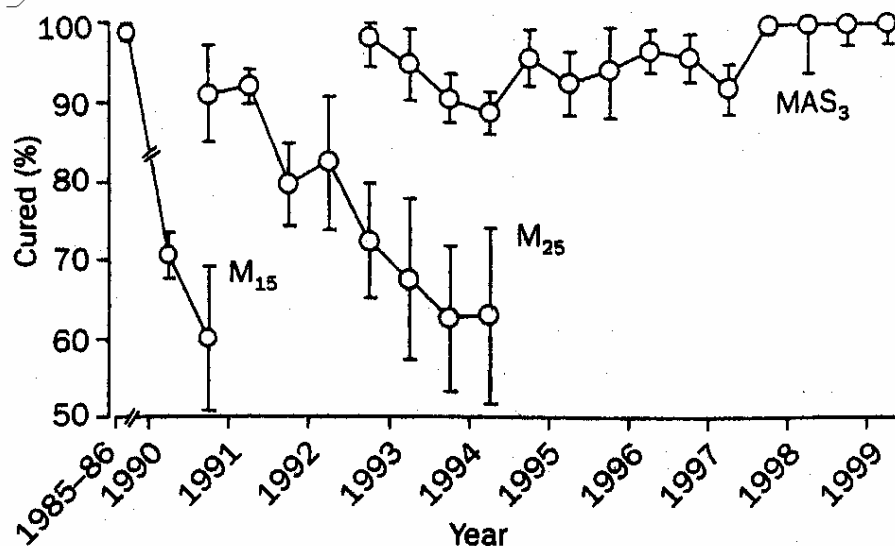
For many years, health organisations and authorities strongly depended on the use of chloroquine as first line therapy of uncomplicated malaria. Steady emergence of resistance to this molecule led to the introduction of the combination sulfadoxine/pyrimethamine (SP). However, resistance to this combination of antimalarial drugs started early to occur in a similar way leaving a dangerous gap in available malaria therapies. In the mid eighties, *P. falciparum* malaria was effectively controlled with the low dose of mefloquine (cure rate with mefloquine 15 mg/kg in 1985 reached 98%), but as mefloquine resistance developed in Southeast Asia, the cure rate fell to 71% in 1990. A similar pattern was seen for high-dose mefloquine monotherapy (25 mg/kg) from 1990-94. The decline in efficacy was accompanied by a rise in the proportions of patients with parent gametocytemia, most probably due to transmission of resistant malaria parasites from patients with recrudescing infections.

Due to this steady loss of formerly fully active antimalarials, combination therapy based on the still highly efficacious artemisinin derivatives (ACTs) has consequently been defined as the new strategy to overcome the problem of resistance development and to combat drug-resistant malaria.

2.5.4.1 Efficacy of artesunate/mefloquine as an ACT

A frequently cited study¹⁷ has confirmed the correctness of the ACT combination concept of therapy. In a prospective study over 13 years, the incidence of *P. falciparum* malaria and the therapeutic responses to mefloquine treatment were investigated on the north-western border of Thailand.¹⁷ More than 10 000 treatments were monitored. Highly multi-drug resistant *P. falciparum* malaria was at this time widely spread in the area. At the beginning of the time of investigation, a standard mefloquine dose of 15 mg/kg was first introduced, followed later by treatment with a higher dose of 25 mg/kg. As a consequence of still emerging resistance of *P. falciparum* against mefloquine, combined artesunate and mefloquine was then introduced as first-line treatment for uncomplicated *P. falciparum* malaria.

Since the general introduction of the artesunate-mefloquine combination in 1994, the cure rate increased again to almost 100% from 1998 onwards (see figure 9).



M₁₅ = mefloquine 15 mg/kg
M₂₅ = mefloquine 25 mg/kg
MAS₃ = mefloquine plus artesunate

Figure 9. Cumulative cure rates (95 % CI), assessed at day 28 for different treatment regimens⁵⁴

Even more importantly, there has been a sustained decline in the incidence of *P. falciparum* malaria in the study area (by 67 % from 1992 to 1997). In-vitro susceptibility of *P. falciparum* to mefloquine has improved significantly ($p = 0.003$)^{17,54} by reduction of resistant strains.

In this area of low malaria transmission, treatment with combined artesunate and mefloquine was able to reduce the incidence of *P. falciparum* malaria and to halt the progression of mefloquine resistance. Furthermore, combination of antimalarial drugs such as mefloquine with artemisinin or a derivative (e.g. artesunate) was shown to protect the drug against resistance.¹¹

A considerable number of clinical studies in uncomplicated malaria were conducted to further evaluate the artesunate-mefloquine combination. Different durations of the therapy with artesunate given for 2 to 5 days combined with mefloquine administered simultaneously or after the last dose of artesunate were investigated. Two days of artesunate followed by mefloquine or a complete therapy over only two days with simultaneous combination tended to be inferior to a therapy concept over a minimum of 3 days. A total artesunate dose of at least 10 mg/kg and mefloquine in a dose 15 to 25

mg/kg, both given in split doses over 2 to 3 days were shown to be of equal importance. A tabular summary of these studies with different doses and administration schedules of artesunate and mefloquine as well as the comparison of the combination with the efficacy of either antimalarial given as monotherapy is presented in Appendix I.

Based on the convincing experiences with all exploratory studies with other ACTs, the combination of artesunate/mefloquine has been promoted as the first-line approach for the treatment and prevention of recrudescence in patients with multidrug-resistant uncomplicated *falciparum* malaria in certain Asian regions. The introduction of both simultaneous or sequential combined artesunate and mefloquine regimen helped indeed to overcome the problem of recrudescence and development of resistance in antimalarial therapy.

Since then, a number of controlled studies further confirmed high efficacy rates and good tolerability for the artesunate and mefloquine combination,^{31,48,53,65,66,67,68} and consequently, it became a standard regimen for the treatment of uncomplicated malaria in some endemic areas like southeast Asia, Peru,^{69,70} Bolivia,⁷¹ India⁷² and Bangladesh.⁷³ However, treatment strategies differed in terms of treatment duration (from one day⁶⁶ to 5 or more days⁶⁷), and in terms of dosing: mefloquine was first customarily introduced only on the second day of the course, because early side effects were suspected. This concern proved to be unfounded as later investigations have shown. A Cochrane evaluation of several studies²⁸ demonstrated superiority of the high mefloquine dose combination over monotherapy with mefloquine in the same total dose regarding efficacy and also safety. In a comparative study in adults,⁷⁴ in the artesunate/mefloquine arm patients were administered artesunate 4mg/kg/day and mefloquine 8mg/kg/day over 3 days (Artequin concept but without pre-packed Co-blister). The 28-day cure rate of 100 % confirmed the clinical suitability of artesunate/mefloquine as ACT. Conventionally, the drugs had to be combined from different packages, which often posed logistical problems and compromised patient compliance.

Rapidly increasing resistance to affordable antimalarial drugs such as chloroquine and sulphadoxine-pyrimethamine in other malaria areas like Africa also necessitated alternative therapy concepts like artesunate/mefloquine as an ACT successfully developed in Asia. This situation has led to an increasingly important role for artemisinin derivatives such as artesunate as one of the most potent combination partners. In order to avoid potential misuse of artemisinin derivatives by broad use in monotherapy and risking their loss through resistance development, it has been suggested also for Africa to replace antimalarial monotherapies by combination therapies like artesunate/mefloquine. Nowadays, to administer an ACT has become the official standard therapy recommendation for uncomplicated *P. falciparum* malaria also for Africa, unfortunately not broadly adapted in practice yet.

To meet the urgent need of potent malaria therapies in Africa, Mepha decided in a first step to start with a combination concept to be realised short-term, namely to combine in Artequin their oral antimalarials already on the market, i.e., artesunate (Plasmotrim tablets) and mefloquine (Mephaquin tablets), in one pre-packed Co-blister suitable for older children and adults able to swallow tablets. Artequin in different dosage strengths has been successfully introduced and also clinically tested in different malaria endemic regions in Africa.. Continuations of this drug development program focussed on

provision of a fixed-dose combination (FDC) of artesunate/mefloquine, in the first instance for the group of small children most vulnerable to malaria and actually without suitable medication to efficiently treat their malaria. As a result of these efforts, a real paediatric formulation of Artequin, the FDC of artesunate/mefloquine in Artequin Paediatric Stickpack, has been realised. There is evidence enough out of the literature and from clinical study programs to substantiate the fact that artesunate/mefloquine as provided in Artequin is a safe and effective ACT also for Africa and should, therefore, officially be recommended as a standard therapy for uncomplicated *falciparum* malaria in all endemic areas. Furthermore, Artequin should substantially contribute, within a reasonably short time, to the replacement of the unacceptably high consumption of artemisinin monotherapies by a well documented high quality ACT, especially in Africa.

2.5.4.2 The Artequin therapy concept

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 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.^{18,19}

2.5.4.2.1 Rationale for the Different Artequin Dosage Formulations

Artequin Co-blister tablet formulations

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.⁷⁵

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. Furthermore, these guidelines clarified that if tolerability is a concern, mefloquine can be given on the first day and that the total mefloquine dose depends on the local sensitivity of the parasite to this drug.

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).

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The Artequin dosage schemes studied in the Artequin clinical trials have been defined in accordance with these WHO guidelines.

Artequin Paediatric

Mepha continuously adapted their ACT development strategy to the WHO recommendations in force at any one time. Considerations regarding the long half-life of mefloquine led to concerns that this may lead to the selection of resistant parasites in areas of high transmission.⁷ As a consequence the recommendation of the higher mefloquine dose has also been advocated for Africa. Therefore, Mepha agreed with the WHO to introduce the high mefloquine dose combinations (Artequin 300/750 and 600/1500) also to East and West African endemic countries. Furthermore, Mepha's new fixed-dose ACT realised in **Artequin Paediatric** contain the higher mean total mefloquine dosage of 25 mg/kg as currently strongly recommended by the WHO for both Asia and Africa. Argumentations to the concept of line-extension of Artequin 600/1500 and 300/750 to a low-dose formulation for small children have been given in 2.5.1 Product Development Rationale. The new concept of Artequin Paediatric has been further investigated in a clinical study described in Section 2.5.4.2.4.

Evaluation of the dose ranges used with Artequin and adaptation to defined patient groups

A current evaluation of all available data from Artequin studies conducted mainly in Africa led to reconsideration of the allocation of proposed Artequin dose ranges to newly defined patient groups as clustered according to their body-weight. As further presented in Section 2.5.4.4.1 and 2.5.5.4.3, a grouping in clusters of 10 – 20 kg, >20 – 40 kg and >40 kg would ideally suite a recommendation of a mean total dose of 12 mg/kg artesunate and 25 mg/kg mefloquine.

2.5.4.2.2 Comparative Phase III studies with Artequin

Asia (Study AM 001-2001)¹⁸

In 2001, a 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: Group A: artesunate 4-5 mg/kg/day and mefloquine 25 mg/kg total dose (~8.5 mg/kg/day; **Artequin-600/1500 and 300/750**) simultaneously; Group B received artesunate 4-5 mg/kg/day and mefloquine 25 mg/kg 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 (see CS 2.7.3.2).

Analysis of the study results revealed a cure rate at day 28 (primary endpoint) of 100% in group A and 99% in group B (difference statistically not significant). The secondary endpoints mean time to fever clearance (group A 34 h vs. B 31 h) and mean time to

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parasite clearance (group A 44 h vs. B 48 h) were similar between groups (both not significant).⁶³

Africa (Study AM 002-2001)¹⁹

Parallel to Study AM 001-2005, 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 French-West Africa. Patients were randomised to receive simultaneous dosing of artesunate 200 mg plus mefloquine 250 mg from the first to the third day (**Artequin®-600/750**), or sequential dosing with artesunate 200 mg/d for three days plus mefloquine 250 mg on the second and 500 mg on the third day (see CS 2.7.3.2).

As already shown in Study AM 001-2005 (“Asian” Study) the cure rate was again similarly high with 100% in the simultaneous dosing group and 98% in the reference group with no recrudescence until day 28. Mean times to fever and parasite clearance were comparable between the simultaneous dosing group and the reference group (32h vs. 26h and 45h vs. 48h, both not significant).

These two studies demonstrate that a 3-day treatment course with artesunate and mefloquine co-administered once daily in identical daily dosages from the first day of therapy (**Artequin concept**) is highly effective in the treatment of acute, uncomplicated *P. falciparum* malaria in both Thailand and in Africa. With 100% success rate, it is as effective and safe as the sequential artesunate and mefloquine treatment regimen (98 to 99%) applied at that time in multi-drug-resistant areas in Asia as well as in regions in Africa with high malaria endemicity.

2.5.4.2.3 Supportive Post-marketing Studies of Artequin in Different Adult and Paediatric Populations

The previously discussed multicentric multinational phase III study conducted with Artequin in French West Africa (Study AM 002-2001) demonstrated high efficacy and good tolerability of an easy to apply dosing concept in adult malaria patients with a body weight range between 30 and 55 kg.

To further investigate the Artequin concept and to extend it to additional patient groups it was to be demonstrated that Artequin was equally useful in African patients with a body weight above 55 kg as well as in children below 30 kg. A series of African studies were consequently conducted with this objective using Artequin 300/375 in children and Artequin 600/750 in adults depending on the patient’s body weight (15 to 30 kg or > 55 kg). These studies followed in general the WHO protocol for assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated *falciparum* malaria (WHO/HTM/RBM/2003.50) and were conducted in compliance with GCP rules regarding, e.g., informed patient’s consent and independent Ethics Committee’s approval. The studies presented were investigator-driven studies. The Artequin formulations investigated were marketed drugs provided by the local Marketing Organisations of Mepha Ltd. (Artequin 300/375, 600/750 or 600/1500 according to the patient’s body weight to reach a mean total mefloquine dose of 15 to 25 mg/kg). Similar endpoints, assessment schedule, and database structure were used in all studies. Five

studies were identified to be analysed for safety aspects.⁷⁶ The efficacy data of these African studies can be summarised as presented in table 1:

Table 1 Investigator-driven post-marketing studies in Africa

Comparative studies:

Location/Investigator	No of patients Treatment	Body Weight/ age	Design*	Efficacy 28-days cure rate
Mali (D. Ogobara) 2005	235 Artequin 300/375	≥ 10 kg/ mean 7.4 (≥ 1) years	o, r, c	96.04 %
	230 Coartem/6	≥ 10 kg/ mean 7.1 (≥ 1) years		96.93 %
Senegal (O. Gaye) 2004	145 Artequin 600/750: for patients >30kg 300/375 for patients 10 to 30 kg	mean 37 (11-110) kg/ mean 15 (2 to 65) years	o, r, c	98 %
	360 Arsucam			97.5 %
	140 Coartem/4			83 %
	149 Coartem/6			100 %
	161 Amod./SP			98.8 %

Open-label studies

Study ART 003-2002: Burkina Faso (R. Guigemde), 2003	53	Artequin 600/750	mean 63.9 (> 55) kg/ mean 25.6 (15 to 57) years	o	100 %
Ivory Coast (Kone M), 2003	50	Artequin 600/750	mean 63 (56-86) kg/ mean 23 (15 to 44) years	o	100 %
Study ART 004-2002: Togo (K. Agbo), 2003	50	Artequin 300/375	mean 23.9 (15- 38) kg/ mean 8.2 (5 to 13) years	o	100 %
Senegal (O. Gaye), 2003	50	Artequin 300/375	mean 24.9 kg/ mean 9.9 years	o	100 %
Kenya (K. Bhatt)	150 50	Artequin 600/750 Artequin 600/1500	31-55 kg > 55 kg Total mean 52.8 kg/ 31.8 years	o	 98.4 %

*db = double-blind; r = randomized; o = open label, c = comparative; Coartem/4, Coartem/6 = four or six dose concept of Coartem; Amod. = Amodiaquine

These post-marketing Artequin studies confirmed overall the results of both phase III studies with high 28-days cure rates of 96 to 100 %. It is of special interest to analyse the Artequin doses administered to the patients relative to the total artesunate and mefloquine doses as calculated according to the patient's body weight per kg. Of the 783 patients enrolled, 779 patients could be evaluated. The results regarding the Artequin dosage as stratified relative to the total artesunate and mefloquine dose per body-weight (age) group can be summarised as shown in table 2:

Table 2 Stratification of the studied population relative to the total artesunate and mefloquine dose per mean body-weight within defined age groups

Total number of included patient files	779	100.0%
Adults (≥ 15 years)	337	43%
Mean weight (kg)	58	
Mefloquine total dose:		
< 12.75 mg/kg	94	12%
15 mg/kg ± 15%	181	23%
17.25 < dose < 21.25 mg/kg	29	3.7%
25 mg/kg ± 15%	33	4.2%
> 28.75 mg/Kg	0	0%
Artesunate total dose:		
< 10.2 mg/kg	137	18%
12 mg/kg ± 15%	185	24%
> 13.8 mg/kg	15	1.9%

Children (< 15 years)	442	57%
Mean weight (kg)	23	
Mefloquine total dose:		
< 12.75 mg/kg	64	8.2%
15 mg/kg ± 15%	173	22%
17.25 < dose < 21.25 mg/kg	100	13%
25 mg/kg ± 15%	97	12%
> 28.75 mg/Kg	8	1%
Artesunate total dose:		
< 10.2 mg/kg	64	8.2%
12 mg/kg ± 15%	173	22%
> 13.8 mg/kg	205	26%
Children (1 to 6 years)	181	23%
Mean weight (kg)	15	
Mefloquine total dose:		
< 12.75 mg/kg	0	0
15 mg/kg ± 15%	64	8.2%
17.25 < dose < 21.25 mg/kg	44	5.6%
25 mg/kg ± 15%	67	8.6%
> 28.75 mg/Kg	6	0.7%
Artesunate total dose:		
< 10.2 mg/kg	0	0
12 mg/kg ± 15%	64	8.2%
> 13.8 mg/kg	117	15%
Children (7 to 14 years)	261	34%
Mean weight (kg)	29	
Mefloquine total dose:		
< 12.75 mg/kg	64	8.2%
15 mg/kg ± 15%	110	14%
17.25 < dose < 21.25 mg/kg	55	7%
25 mg/kg ± 15%	30	3.8%
> 28.75 mg/Kg	2	0.25%
Artesunate total dose:		
< 10.2 mg/kg	64	8.2%
12 mg/kg ± 15%	109	14%
> 13.8 mg/kg	88	11.3%

The major part of patients was in the artesunate total dose range of 12 mg/kg ± 15 %, , thus in line with the dosage recommendation for this ACT (mean total artesunate dose of 12 mg/kg). At the time of investigations in the early 2000s, the official dosage recommendation for mefloquine in the 3-days therapy concept with artesunate/mefloquine was 15 to 25 mg/kg total dose for partially immune patients in Africa. Therefore, Artequin 300/375 and 600/750 were mainly used in these investigator-driven post-marketing studies (with the exception of the Kenya study where patients with >55 kg body weight received the high mefloquine dose Artequin 600/1500). These dosage schemes are reflected in the proportion of patients clustered in different dosage groups. In the whole group of patients near to 80 % received a mefloquine dose between 13 and 29 mg/kg with a summit at 15 mg/kg. Very informative is the clustering of the children treated with Artequin. Out of a total of 442 cases, 205 children can be grouped into a high mefloquine dose Artequin therapy, i.e., 100 received a total mefloquine dose between 17 and 21 mg/kg; another 97 had a mean dose of 25 mg/kg, which exactly represents the dose currently requested by the WHO also for Africa. 8 further children were even dosed with over 28 mg/kg mefloquine. Important to note, that irrespective of the dosage of mefloquine administered in combination with artesunate, in all dosage groups the efficacy rate as defined by the 28-

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day cure rate, was near or equal to 100 % (see table 1) demonstrating that with the Artequin concept currently used, there was never an efficacy issue to be mentioned. Therefore, with the FDC of Artequin Paediatric developed with the high mefloquine dose concept (i.e., mean total dose of 25 mg/kg) an equally high efficacy rate was expected and subsequently demonstrated in Study AM-P 001-2005 as described below.

2.5.4.2.4 Rationale for the Artequin dosage strengths in relation to the patient's body-weight ranges

The African phase III study AM 002-2001 was conducted in adult (and few children) malaria patients with a body weight range between 30 and 55 kg treated with Artequin 600/750. This range was further expanded in the post-marketing trials to 15 – 30 kg in children treated with Artequin 300/375 and > 55 kg in adults treated with Artequin 600/750 and Artequin 600/1500. These doses still followed the WHO guidelines in force in the early nineties⁸⁵ recommending 15 to 25 mg/kg total mefloquine dose for partially immune patients living in high transmission endemic areas.

It is of special interest to group these patients relative to the mefloquine total doses really administered. This will give a basis for the definition of a reasonable new dosage proposal for the currently recommended high-dose mefloquine formulation of the combination. Patients should be allocated to therapy groups based on their body weight, since both antimalarials, artesunate and mefloquine, are usually dosed based on this parameter.

The following presettings can be named as basis for further considerations:

- patients grouped following the age can be put in relation to their respective body-weights
- following current WHO recommendations, an artesunate/mefloquine combination with a total mefloquine dose of 25 mg/kg has to be applied
- the whole set of 779 evaluated patients out of the African post-marketing Artequin studies forms a sound basis of information regarding real doses administered

Following considerations can be linked together:

- ↪ A generally accepted grouping of patients with respect to age defines a range of 1 to 6 years for small children or “infants”, that of 7 to 14 years as children at school or “pupils and one over 14 years for adolescents/adults (Roche Lexicon of Medicine). For this Clinical Overview, paediatric patients are of special interest. Following the above ranges of age, a total of 442 children can be identified as described in table 2.
- ↪ The children in the group of 1 to 6 years had a mean body weight of 15 kg, those in the group of 7 to 14 years one near to 30 kg. Table 3 illustrate the wide distribution of the total mefloquine dose really administered. This distribution reflects the Artequin dosage strengths mainly administered as described above. A new grouping of the patients to better meet the current dose recommendation is obviously needed.

Table 3 Grouping of children regarding age and total mefloquine dose

Children 1-6 years					
Total of children 1-6 (N=181)	< 12.75 mg/kg (N=0)	15 mg/kg ± 15% (N = 64)	17.25 < dose < 21.25 mg/kg (N = 44)	25 mg/kg ± 15% (N = 67)	> 28.75 mg/kg (N=8)
Children 7-14 years					
Total of children 7-14 (N=261)	< 12.75 mg/kg (N=64)	15 mg/kg ± 15% (N = 110)	17.25 < dose < 21.25 mg/kg (N = 55)	25 mg/kg ± 15% (N = 30)	> 28.75 mg/kg (N=2)

A total of 206 children received in the artesunate/mefloquine combination of Artequin a mefloquine dose of at least 17.25 mg/kg corresponding to 119 “infants” and 87 “pupils”.

- ↪ According to the current WHO recommendations, a total dose of 25 mg/kg mefloquine (in Artequin) should be applied to the therapy groups with a mean body-weight of 15 and 30 kg, respectively, leading to total mefloquine doses of 375 and 750 mg in the respective therapy groups.
- ↪ Based on the available clinical data, for mefloquine a therapeutic dose range of 25 mg/kg ± 25% can be accepted leading to a total mefloquine dose between 18.75 and 31.25 mg/kg
- ↪ With a total mefloquine dose of 375 and 750 mg, respectively, this dose range corresponds to a calculated body-weight range of 10 and 20 kg for children of 1 to 6 years (mean body weight 15 kg) and of >20 to 40 kg for children of 7 to 14 years (mean body weight 30 kg), respectively

Following this definition of therapy groups, a total of 201 children have already been treated in the post-marketing studies within the high mefloquine dose-range administered with Artequin as shown in table 4 giving more information to the acceptability of the proposed grouping as defined above.

Table 4 Grouping of children regarding body-weight and total mefloquine dose

Body weight 10-20kg mean 15 kg (N=206)			Body weight >20-40 kg mean 29 kg (N=226)			Body weight >40kg mean 58 kg (N=347)*		
Total of patients (N=206)	< 18.75 mg/kg (N=55)	≥ 18.75 mg/kg (N=151)	Total of patients (N=226)	< 18.75 mg/kg (N=176)	≥ 18.75 mg/kg (N=50)	Total of patients (N=347)	< 18.75 mg/kg (N=301)	≥ 18.75 mg/kg (N=46)

- ↪ The currently available Artequin dosage strength started at the beginning of development with Artequin 600/1500 in line with the actual total dose of 600 mg artesunate and 1500 mg mefloquine widely used for adults in South East Asia in

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the late eighties, early nineties for this combination. Artequin 600/1500 was consequently down-scaled in a dose-linear way to Artequin 300/750 and finally, to Artequin Paediatric with a total dose of 150 mg and 373 mg of the respective active ingredients. Calculating the total mefloquine dose ranges which can be achieved with this Artequin preparations, it is apparent that these dosage strengths are well suitable for the treatment of patients in the respective treatment groups, namely adolescents/adults of > 40 kg, children with >20 to 40 kg and 10 to 20 kg, respectively, and provide a dosage within the acceptable mefloquine dose range.

The body-ranges of 10 to 20 kg for Artequin Paediatric and consequently, one of >20 to 40 kg for Artequin 300/750 were defined for the African study on paediatric populations as described in the following Section.

2.5.4.3 Efficacy of Artequin in Paediatric Populations (Study AM-P 001-2005)

The clinical success of the Artequin therapy concept as presented above gave support to expand the Artequin dosage ranges further to a therapy also suitable for small children for whom acceptable paediatric formulations are currently lacking. The new FDC of Artequin Paediatric Stickpack presented in this Overview is a dose-linear line-extension of the “high mefloquine dose” Artequin Co-blister tablet formulations, namely Artequin 600/1500 for adults and Artequin 300/750 for children.

Study AM-P 001-2005 was an open-label, stratified investigation on the pharmacokinetic and pharmacodynamic characteristics of the combination of artesunate and mefloquine given daily for 3 days in the fixed-dose combination (Artequin Paediatric Stickpack) and in the Co-Blister (Artequin 300/750) to children (stratified in two body weight groups) with uncomplicated *Plasmodium falciparum* malaria. Each patient with a body weight of 10-20 kg (n = 41) received the fixed-dose combination of artesunate 50mg and mefloquine 125mg in a Stickpack once daily for 3 days. Each patient with a body weight of >20 to 40 kg (n = 30) received a dose of Artequin 300/750, i.e., the Co-Blister formulation of artesunate 100mg and mefloquine 250mg once daily for 3 days (for detailed information on the conduct and outcome of this study see CS Section 2.7.3.2).

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 their respective target population (i.e., 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). 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. No significant differences between treatment group A and treatment group B in the 28-day cure rate were demonstrated.

Time to parasite clearance was short (median 36.0 hours overall and for treatment A, 35.9 hours for treatment B) and did not appear to differ greatly. These values are clinically acceptable for both groups (figure 10).

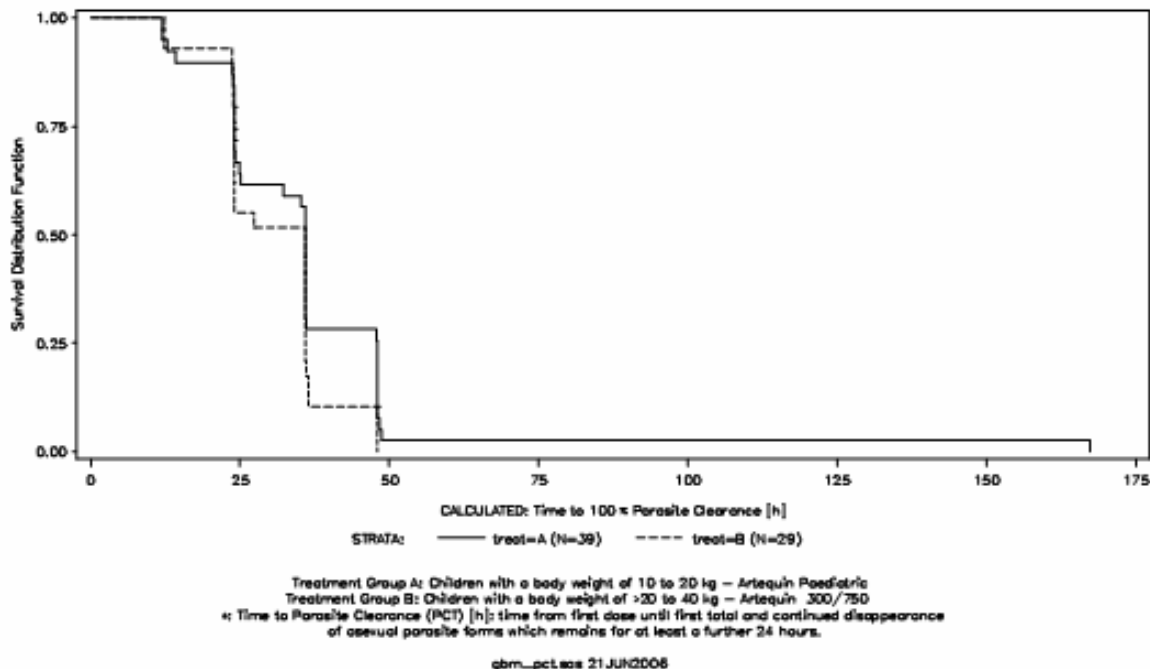


Figure 10 Time to parasite clearance per treatment group

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 28 out of 29 in treatment group B (96.6%).

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/ μ l) 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 (figure 11).

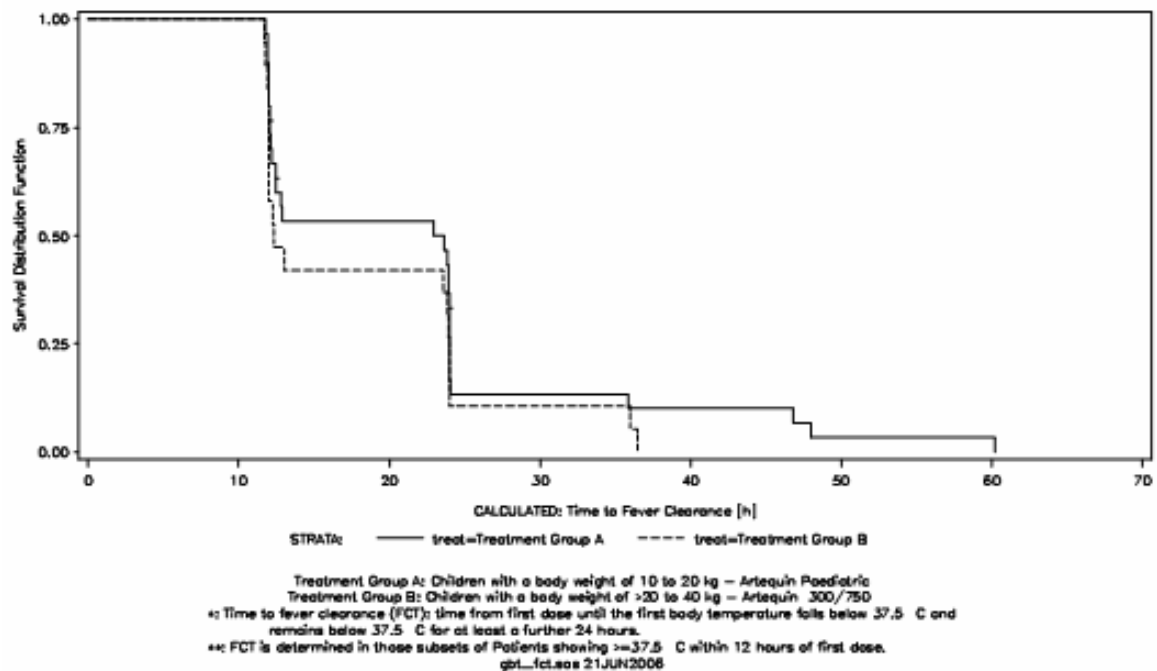


Figure 11 Time to fever clearance per treatment group

3 patients withdrawn from the population have to be considered for the efficacy analysis. Of these patients, one of group A had to be withdrawn due to diagnosis of severe malaria on day 2 based on appearance of convulsions. Another patient of group A suffered vomiting interfering with the intake of oral medication, a frequent event in all paediatric treatments and a third of group B received rescue medications only due to purely technical problems in the interpretation of a thick blood slide. Therefore, these patients did not detract from the effect of the medication.

Acceptability of intake of study medication is of great importance in paediatric patient populations. Acceptability in the total study group was rated as excellent in 83.1% on day 1, 77.5 % on day 2 and 81.7 % on day 3. There was no significant difference of the rating between the two groups, although acceptability in group A was somewhat lower most probably due to the lower age in this group often associated with more difficulties in medication intake in general (two assessments were rated as poor, both by small children of group A).

Pharmacokinetic results were generally in line with the published data and allow to forecast, within the anticipated limitations of the sample size and the very sparse sampling schedule used for mefloquine that appropriate drug plasma concentrations for the treatment of *Plasmodium falciparum* infection are reached with both treatments and in the case of mefloquine maintained for the 28 days observation period or close to it and thus, both profiles showed appropriate and very similar pharmacokinetic characteristics (see also CO 2.5.2 Overview Biopharmaceutics).

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The high healing rates of 100% in both groups of children are in line with those demonstrated in the post-marketing studies (see above: Efficacy of Artequin in Adult and in Paediatric Populations) as well as in the randomized, comparative Phase III studies with different Artequin dosages.^{18,19} The newly defined body-weight ranges, e.g., >20 to 40 kg for Artequin 300/750 are at the higher end slightly above the previously defined range of 25 to 35 kg in children. Therefore, children with a BW of 40 kg actually receive a slightly reduced total dose regarding mefloquine as the combination partner in Artequin. Nevertheless, in none of the groups in the post-marketing studies treated with different doses was any efficacy issue to be recorded thus demonstrating, that the doses as proposed in the new dosage concept are high enough to guarantee full efficacy of therapy.

Based on the literature review as well as on the positive outcome of all Artequin studies conducted, there is sufficient evidence to state that the efficacy of the combination of artesunate/mefloquine is equally proven for both Asia and Africa and should be recommended as standard ACT in these malaria endemic regions.

Similarity in clinical outcome with both Artequin formulations confirms that down-scaling from Artequin 300/750 to the dose-linear FDC of Artequin Paediatric as a line-extension has successfully been realized. Therefore, Artequin Paediatric can be administered without reservations to small children in their respective target group of 10 to 20 kg of body-weight. Nevertheless, as generally requested for all antimalarials to monitor possible development of resistance and as a consequence decrease of therapeutic activity, further surveillance of the efficacy of this drug urgently needed in this patient group of small children has to be advocated. Therefore, post-marketing monitoring of the broad use in children with uncomplicated *falciparum* malaria has to be planned and realized, preferably in different African malarial endemic regions.

2.5.5 Overview of Safety

The adverse events experienced by patients taking antimalarial drugs often mirror the symptoms of malaria. Nowadays, it is accepted that a major part of the AEs reported in investigations with antimalarials used in monotherapy or in combination are attributable to the disease to be treated, i.e., malaria.⁷⁷ As long as the safety profile of either drug in the combinations is well defined, it is also possible to manage adverse events. This is the case for both artesunate and mefloquine, antimalarials already successfully used for decades in treatment of uncomplicated *falciparum* malaria. Clinically relevant safety aspects of both artesunate and mefloquine used in monotherapy or in combination are discussed below.

2.5.5.1 Undesirable effects reported with artesunate monotherapy

Animal studies have documented CNS toxicity with artemisinin derivatives. In particular, parenteral administration of high doses of arteether and artemether resulted in a peculiar selective pattern of damage to the brain stem, especially the reticular formation, the vestibular system nuclei and nuclei related to the auditory system.⁷⁷ Neurotoxicity is most probably determined by the pharmacokinetic properties of the drugs. Sustained CNS exposure from slowly absorbed or eliminated artemisinins (e.g., delayed absorption from the oil based parenteral formulations of arteether and artemether) is considerably more neurotoxic than intermittent brief exposure as is the case with the oral administration of these drugs or of artesunate given by any route. In fact, it has been shown that parenteral artesunate is significantly less neurotoxic than intramuscular artemether in a mouse model of neurotoxicity.⁷⁸ Despite the pre-clinical findings of brainstem toxicity in animals, millions of doses in various formulations have been given to humans without significant evidence of major toxicity, even when particular attention is given to monitoring for neurotoxicity both clinically and pathologically.²⁴

The most commonly reported adverse effects of artesunate monotherapy (total oral dose of 600 mg to 1200 mg) are nausea (incidence rate between 14 and 45%), vomiting (19 to 26%) and diarrhoea 4 to 10%), all of which are also characteristic of acute malaria.

Other adverse effects reported in clinical trials in smaller number of patients included dizziness, itching, abdominal pain, flatulence, headache, body ache, tinnitus, convulsion, and transient slight reduction in neutrophil counts.⁷⁹ It is important to note that these adverse effects may be disease- rather than treatment-related. The observation that there were no adverse effects in any patient is in accordance with findings in some other studies.⁸

There are several early reports on the use of artemisinin derivatives during pregnancy.^{80,81} Although foetal resorption in rats occurs at relatively low doses, none of these studies in humans has found any evidence of foetal and maternal toxicity. A later study on 461 pregnant women (including 44 first-trimester episodes) treated with artesunate or artemether showed that artemisinins were well tolerated with no evidence

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of adverse effects in women and neonates. Birth outcome did not differ significantly to community rates for abortion, stillbirth, congenital abnormality, and mean gestation and delivery.⁸² A further study compared the therapy outcome of a combination of artesunate/mefloquine with that of quinine in second to third trimester pregnant women suffering from *falciparum* malaria. In both therapy groups, physical and neurological development of the babies were normal and there were no congenital abnormalities in either group (n = 28 in the artesunate/mefloquine group).⁸³ In 2003 the WHO published an assessment on the safety of artemisinin compounds in pregnancy (WHO/CDS/MAL/2003). Published data on 607 pregnancies in which artemisinin compounds were given during the 2nd or 3rd trimesters gave no evidence of treatment-related, adverse pregnancy outcomes. Similar data show normal outcomes in 124 pregnancies exposed to artemisinin compounds in the 1st trimester. For an overall final conclusion, these numbers may have been at this time too small to provide an adequate profile of the safety of these compounds when used to treat malaria in pregnancy. Therefore, further investigations have to be initiated to additionally exploit the potential use of artemisinins, and consequently of their combinations in pregnancy. Nevertheless, one has to take into considerations that *falciparum* malaria in pregnancy poses substantial risk to a pregnant woman and her neonate through anaemia and low birth weight. Thus, current evidence out of all study data and, especially the necessity of a broad use of artemisinins in endemic regions most often in coincidence with malaria and pregnancy, justify the use of artesiminins like artesunate also in pregnant women. A formal monitoring programme, e.g., in antenatal care clinics and delivery units is a need to compile further evidence of the safety of artemisinin compounds in pregnancy. All pregnant women treated with artemisinin compounds should be carefully followed up to document the pregnancy outcomes and subsequent development of the child and reported to the appropriate authorities.

The safety profile of artesunate is well known and tolerability is in general judged as very good. No unexpected adverse events have to be expected during the short term administration as defined for the ACTs and, in particular, within the combination concept of Artequin in which the tolerability is mainly determined by the combination partner mefloquine.⁷⁸ Severe AEs are hardly ever to be expected with the exception of very rare allergic reactions which can occur in any kind of drug therapy.⁷⁸ Although pregnancy is not an issue in context with the use of Artequin Paediatric due to the low age of the target population, as a precaution for the possible of-label use in women of childbearing age, the above information to the use of artemisinins in pregnancy has to be taken into consideration.

2.5.5.2 Undesirable effects reported with mefloquine monotherapy

Mefloquine monotherapy is generally well tolerated at doses used for the prophylaxis and treatment of malaria. The most frequently reported adverse effects are nausea, vomiting, soft stools or diarrhea and abdominal pain, dizziness or vertigo, disturbed sense of balance as well as neuropsychological adverse effects such as headache, somnolence and sleep disorders (sleeplessness, unusual dreams).

Severe neuropsychiatric adverse events (including seizures and organic psychosis) were recorded in isolated cases and have been broadly discussed in the mid nineties in

public media, especially by campaigners in the UK. These topics are regularly taken up by journalist causing overestimation of such events. Whether such events are pharmacological reactions is still unclear. The real importance and incidence of these adverse reactions have been evaluated in full. The incidence of serious neuropsychiatric symptoms is in fact low with a rate of approximately 1 : 10000 which is about the same rate as with chloroquine. There should be a dose-related element to this group of adverse events, which did not become apparent until now. It is important to note, that the background incidence of severe neuropsychiatric disorders in the general population is higher than the rates among users of mefloquine for the indications given, rendering an estimate of causal relationship very difficult.^{17,84}

Both seizure and psychosis are recognized adverse effects and it is sensible to avoid using this drug in predisposed patients if possible (e.g. in epileptic patients). Avoidance of use in the setting of chemoprophylaxis is certainly possible, since alternatives exist. In the setting of *falciparum* malaria, which is a life-threatening illness, the benefits may outweigh the risks in this subgroup of patients. Furthermore, other antimalarial drugs, which might be used as alternatives, may also carry the risk of precipitating a seizure.²⁶

Even though pregnancy is not an issue in context with the use of Artequin Paediatric considered for the administration in small children with an approximate age of up to 6 years, for an unintended use in women of childbearing age, the following informations have to be borne in mind. Fetal damage was seen in mice and rats given 5-20 times the recommended human treatment dose daily during early pregnancy. There is no evidence that mefloquine is associated with teratogenicity in humans.⁸⁵ However, it seems sensible to avoid the drug whether possible, especially during the first trimester. This advise is, however, difficult to follow especially in rural regions of developing countries where malaria infection and pregnancy cannot really be separated from each other. Taking into consideration the lack of evidence for teratogenicity of mefloquine in humans, therapeutic use of this antimalarial in pregnancy is certainly justified. In fact, an unplanned pregnancy during malarial administration of mefloquine was never considered to be an indication for abortion.

Mefloquine is generally well tolerated by malaria patients. From the most reported AEs like gastrointestinal or CNS symptoms, approximately one-third can be ascribed to the malaria itself.

2.5.5.3 Undesirable effects reported with the combination of artesunate and mefloquine:

When artesunate is used in combination with mefloquine, the adverse effects attributable to one or the other antimalarial drugs are even more difficult to analyse and quantify. Vomiting is of major concern in such combined regimen as mefloquine-induced vomiting of the administered drug is an adverse event that has been associated with treatment failure.¹¹

In one study,⁶⁵ combination therapy with artesunate and mefloquine caused a statistically non significant, i.e., slightly higher incidence of vomiting (26%) than did treatment with either individual drug (19% with artesunate alone and 16% with mefloquine alone). On the other hand, in a large number of patients other investigators

found that the combination of artesunate and mefloquine was associated with lower incidence of vomiting than mefloquine alone.^{62,67} In 652 Thai patients, the incidence of vomiting within 1 hour of administration of the total dose of 25 mg/kg mefloquine given in one single dose was reduced by one-half when this dose of mefloquine was given 24 hours after artesunate.⁶²

Nausea and dizziness were more frequent in patients receiving mefloquine alone than in those receiving it in combination with artesunate.⁶⁷

Other possibly drug-related adverse effects (e.g. headache, abdominal pain) appear to occur with a similar frequency in patients receiving combination and in those receiving either drug as monotherapy.

In contrast to these findings, Price et al.⁴⁹ reported that patients receiving a combined regimen of mefloquine plus an artemisinin derivative (either artesunate in 630 patients or artemether in 206 patients) were associated with significantly more ($p < 0.001$) side effects than those with an artemisinin derivative alone; acute nausea (31% versus 16%), vomiting (24% versus 11%), anorexia (51% versus 34%), and dizziness (47% versus 15%). There was no evidence that either derivative caused allergic reactions, neurologic or psychiatric reactions, or cardiovascular or dermatologic toxicity. The high incidence of AEs in the combination groups may strongly be affected by the mode of co-administration of mefloquine. It is important to see, that only 4 % of patients in the combination groups received mefloquine in a split dose (15 mg/kg on admission and 10 mg/kg 8-24 hours later). All remaining patients received 25 mg/kg mefloquine as a single dose either on admission (21 %), on day 1 (7 %) or thereafter (68 %). Such study results led to the claim to split the mefloquine total dose into a sequential administration on days 2 and 3 of the 3-days artemisinin therapy or even given in 3 equal daily doses over 3 days in parallel to the daily artemisinin doses. The Cochrane evaluation²⁹ cited in Sections 2.5.4 demonstrated superiority of the high mefloquine dose combined with artesunate over monotherapy with mefloquine in the same total dose regarding efficacy and also safety. The different PK characteristics of the two combination partners may offer an explanation. Even with simultaneous administration of both drugs from the first day on, maximum mefloquine plasma concentrations are achieved after a mean of 17 hours, i.e., in a period of recovery from the malarial symptoms due the short but fast acting combination partner artesunate which at this time already reduced the parasite load to a high extent.

These considerations are further put into perspective with the different Artequin study results mainly out of Africa, as further demonstrated and discussed in the Sections below.

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2.5.5.4 Undesirable effects reported in clinical studies on patients treated with Artequin

2.5.5.4.1 Artequin Studies Phase III

In the Artequin study AM 001-2002,¹⁹ one third of the Asian patients experienced adverse events (AE). The system organ classes most commonly affected were "metabolism and nutritional disorders", "gastrointestinal disorders", and "nervous system disorders". No AE showed a statistically significant difference in occurrence between treatment groups. Early vomiting occurred in only two patients who received artesunate and mefloquine simultaneously from the first day on (Artequin). In particular, there was no difference in the overall incidence of vomiting.

There were no clinically meaningful differences between the treatment groups for any of the haematological and biochemical parameters at baseline and during the course of the study. However, in few patients in both treatment groups (difference not significant) hypokalemia was rated as AE, most likely caused by malaria induced disturbances of the water-electrolyte balance.

Moreover, no clinically significant changes of vital signs and ECGs were noted during the study.

All patients had regular specific neurologic examinations during the study. There was no patient with an abnormal neurological finding.

The overall tolerability of the treatment as assessed by the investigators at day 28 was judged to be "very good" for almost all patients in both treatment groups.

Regarding safety findings in the Artequin study AM 002-2002,²⁰ approximately half of the African patients experienced one AE during the study. The system organ classes most commonly affected were the gastrointestinal tract, general disorders and nervous system disorders. Many potential adverse effects of the anti-malarial drugs were most likely related to the underlying malaria disease. As already discussed at the end of Section 2.5.5.3, this Artequin study in Africa confirmed that the co-administration of both drugs from the first day on did not translate into increased mefloquine-related AEs like vomiting as it has been described in the literature.^{62,86} The incidence of vomiting was actually statistically significantly lower in the simultaneous group (Artequin) than in the sequential one ($p = 0.014$). Dizziness was numerically higher in the latter group than in the sequential group, however, this finding did not reach statistical significance ($p=0.138$). All other AEs showed no relevant statistical differences in occurrence between treatment groups.

No clinical relevant findings or differences between study groups were observed in the ECG and vital signs assessments as well as for laboratory evaluations.

Overall tolerability of the treatments as assessed by the investigators at day 28 was judged to be very good in two thirds of the patients in both treatment groups.

Information regarding safety and tolerability of Artequin described in clinical studies conducted with this drug have been accordingly translated to the SmPC of Artequin Paediatric.

2.5.5.4.2 Safety of Artequin Paediatric and Artequin 300/750

The overall tolerability of two study formulations was investigated in Study AM-P 001-2005 in children with uncomplicated *Plasmodium falciparum* malaria (Artequin Paediatric/treatment group A; BW 10-20 kg and Artequin 300/750/treatment group B; BW >20-40 kg) (see also CS Sections 2.7.4.1.1 and 2.7.4.2.1.1). Due to the similarity of the PK characteristics of both study medications, similar drug exposure in both groups can be concluded. Therefore, Safety characteristics in the paediatric study population as a whole are first discussed and put into perspective with the different study groups only if appropriate.

Twenty-five patients (25.2 %) had one adverse event judged as related to the study medication, with more patients in treatment group B than treatment group A. Most AEs were mild, with only a fourth reaching moderate severity. No AEs related to the study medication were rated as severe or serious.

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. Regarding differences between treatment groups, diarrhoea was more frequent in group A, probably due to their younger age and thus, higher susceptibility to concomitant metazoan parasites infestation. Group B patients were more likely to suffer from headache, abdominal pain and dizziness. Differential likelihood of reporting might have played a role in the observed differences - older children are more likely to verbalise their complaints.

Haematological abnormalities were frequent at baseline. They mostly consisted in decreases in haemoglobin, haematocrit and RBC with increased reticulocytes that are the expected changes of a haemolytic anaemia as those induced by *falciparum* malaria. Concomitantly, neutrophil percentages tended to be high, eosinophil percentages to be lower than at later time-points and platelet counts to be low. These changes are also expected consequences of *falciparum* malaria. Frequent infestations by metazoan parasites in the study population further hamper the interpretation of the haematological values.

Regarding clinical chemistry tests, most abnormalities were not clinically significant. Only exceptions were:

- An increase in serum transaminases up to 271.00 U/L for SGOT as compared to an upper normal limit of 19.00 U/L and of SGPT up to 197.00 U/L as compared to an upper normal limit of 23.00 U/L, peaking on day 3 but already present before treatment. Therefore, it was probably due to an intercurrent condition but an aggravation due to the study drug cannot be completely ruled out.
- Two cases of increases in plasma triglycerides, 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. The mechanism leading in some cases of malarial infection to increased TG values is not fully clarified. *Plasmodium falciparum*

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malaria has been reported to be associated to changes in lipid parameters.⁸⁷ Isolated increases of TG have been found in Gabonese children with low levels of parasitaemia.⁸⁸

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

No severe nor serious Adverse Events related to the study medications have been reported. Thus, the Study AM-P 001-2005 shows appropriate safety profiles for both treatments in their respective target population with similar safety profiles again as compared to the outcome of other Artequin studies with different dosages and target populations including children and adults with uncomplicated *P. falciparum* malaria. This comparison is even more important considering the fact that the study medications investigated in Study AM-P 001-2005 contained the higher mean total mefloquine dosage of 25 mg/kg as currently strongly recommended by the WHO for both Asia and Africa.

2.5.5.4.3 Post-marketing Artequin Studies in Africa

Additional post-marketing studies in African patients were carried out to further investigate the use of Artequin in children below 30 kg as well as in adults with a body weight above 55 kg (Artequin 300/375 in children and Artequin 600/750 in adults depending on the patient's body weight). The Safety data of the African post-marketing studies have been accurately analysed⁷⁷ and can be discussed as follows:

Adverse Events categorised by the investigators as such and Treatment or Follow-up observations occurring or worsening after start of the therapy but not categorised by the investigators as AEs (symptoms in general related to the malaria infection per se) were carefully grouped and analysed separately. Following questions are of special interest:

- Is the incidence of AEs consistent with the scale expected (comparison with the literature and with the outcome of the Artequin Studies AM 001-2001, AM 002-2001 and AM-P 001-2005)?
- Is there any difference in the incidence of AEs based on the dosage range of Artequin administered (with special emphasis on the total mefloquine dose)?
- Is there any difference in the incidence of AEs based on the age (body-weight) group of patients treated with Artequin?

Incidence of AEs in comparison to literature and clinical studies data

Gastrointestinal disorders like abdominal pain, nausea, vomiting and diarrhoea have been reported in the Artequin clinical studies the most frequently but with a lower incidence as compared to the findings achieved with the combination artesunate and single high dose mefloquine as described by Price et al.⁴⁹ and discussed above. A

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similar incidence was also shown regarding nervous system disorders, in particular headache, dizziness and insomnia as well as regarding general and metabolism disorders like asthenia, anorexia and hypokalemia. As summarised in CS Section 2.7.4.2.1.5, a lower incidence of gastrointestinal symptoms has been found in Asian patients as compared to those in Africa (approximately 10% as compared to 17.3%). The African paediatric population showed a higher incidence in the group of older children (BW >20 – 40 kg), i.e., 22 vs 40%. In the post-marketing Artequin studies, an overall lower incidence of gastrointestinal AEs has been reported, with a tendency to slightly less symptoms in the group of small children (1 – 6 years of age). A similar proportion of nervous system disorders have been found across the Artequin studies evaluated, but with an apparently more pronounced tendency to increase with dose. It has to be taken into consideration that the different treatment groups in the phase III Artequin studies overlap within the respective body-weight ranges. Taking the ranges as defined in Section 2.5.4.2.4, i.e., grouping regarding BW less or more than 40 kg, show that differences in the incidence of AEs most probably reflect isolated cases and cannot substantiate any trends towards a dose-dependency of the CNS symptoms (see also CS Section 2.7.4.5.1).

Most of these adverse events were of mild to moderate severity and occurred in fact with a similar frequency, when historically compared to the incidence rate of adverse events observed in patients receiving either drug as monotherapy.^{62,65}

There were no unexpected observations regarding nature and incidence of AEs reported in the African post-marketing Artequin studies.

Incidence of AEs in relation to the dosage range of Artequin

The patients treated in the post-marketing African studies have been clustered in different dosage groups of Artequin as defined by the total dose of mefloquine administered. Table 5 presents all children (N=442) split into two groups of 1 to 6 and 7 to 14 years of age, respectively, and displayed in the respective dosage categories. Gastrointestinal and neurological/psychiatric symptoms represent the two groups of AEs with higher incidence and are shown in the table. Symptoms reported in few scattered cases like dermatological and musculoskeletal are not presented. Typical symptoms of malaria like asthenia, fatigue, fever, headache, malaise, shiver or sweating reported as general symptoms and syndromes are not relevant for the discussion of AEs described as drug related and are, therefore, likewise omitted. There were no cardiac, infectious or pulmonary/upper respiratory symptoms reported in the group of children.

Table 5 Incidences and number of patients with adverse events for each category according to children age groups and displayed by mefloquine total dose per body weight:

Categories of events	Children 1-6 years					
	Total of children 1-6 (N=181)	< 12.75 mg/kg (N=0)	15 mg/kg ± 15% (N = 64)	17.25 < dose < 21.25 mg/kg (N = 44)	25 mg/kg ± 15% (N = 67)	> 28.75 mg/kg (N=8)
	Gastrointestinal	17% (31)	0% (0)	18.7% (12)	18.1% (8)	16.4% (11)
Neurological and psychiatric	1.6% (3)	0% (0)	0% (0)	6.8% (3)	0% (0)	0% (0)
	Children 7-14 years					
	Total of children 7-14 (N=261)	< 12.75 mg/kg (N=64)	15 mg/kg ± 15% (N = 110)	17.25 < dose < 21.25 mg/kg (N = 55)	25 mg/kg ± 15% (N = 30)	> 28.75 mg/kg (N=2)
	Gastrointestinal	10.3% (27)	4.6% (3)	9% (10)	16.3% (9)	16.6% (5)
Neurological and psychiatric	4.6% (12)	1.5% (1)	4.5% (5)	9% (5)	3.3% (1)	0

No relevant dose-dependency of the gastrointestinal symptoms can be derived from the distribution of the events over the different dosage ranges. These symptoms are also difficult to distinguish from the symptoms of the malarial disease and cannot be defined as drug-related with certainty.

The number of patient in the older children treated with the highest dose is too small to allow any comparison regarding the occurrence of neurological/psychiatric events. The marginal difference in the reported events between the two groups of children may to some extent be explained by the possibility that older children are more likely to report unwanted effects experienced during the therapy. The same observation has been done in the group of older children in the Artequin study in paediatric patients (AM-P 001-2005). Neurological and psychiatric events are described also in context with both artesunate and mefloquine monotherapy and are, therefore, not unexpected observations.

Incidence of AEs in relation to the age (body-weight) group

As discussed in Section 2.5.4.2.4, body-weight ranges of 10 – 20 kg and >20 – 40 kg in children and one of >40 kg in adolescents/adults were defined to comply best with the recommended dosage of Artequin containing the high mefloquine mean total dose of 25 mg/kg. Table 6 presents these body-weight categories together with the respective incidence of symptoms in both children and adults.

Table 6 Incidences and number of patients with adverse events for each category according to body weight groups and focussed to mefloquine total dose above 18.75 mg/kg

Categories of events	Body weight 10-20kg (N=206)			Body weight >20-40 kg (N=226)			Body weight >40kg (N=347)*		
	Total of patients (N=206)	< 18.75 mg/kg (N=55)	≥ 18.75 mg/kg (N=151)	Total of patients (N=226)	< 18.75 mg/kg (N=176)	≥ 18.75 mg/kg (N=50)	Total of patients (N=347)	< 18.75 mg/kg (N=301)	≥ 18.75 mg/kg (N=46)
Cardiac	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	4.3% (14)	2.6% (8)	13.0% (6)
Dermatological	1.4% (3)	3.6% (2)	0.6% (1)	0.9% (2)	0.6% (1)	2.0% (1)	0.6% (2)	0.7% (2)	0% (0)
Gastrointestinal	16.5% (34)	21.8% (12)	14.5% (22)	10.1% (23)	6.8% (12)	22% (11)	22.7% (79)	20.9% (63)	34.7% (16)
General symptoms and syndromes	11.6% (24)	18.1% (10)	9.3% (14)	3.5% (8)	1.1% (2)	12% (6)	20.7% (72)	18.6% (56)	34.7% (16)
Infectious	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0.3% (1)	0.3% (1)	0% (0)
Musculoskeletal	1.0% (2)	0% (0)	1.3% (2)	1.7% (4)	0.6% (1)	6.0% (3)	0.9% (3)	1.0% (3)	0% (0)
Neurological and psychiatric	1.4% (3)	0% (0)	2.0% (3)	5.3% (12)	1.7% (3)	18% (9)	33.1% (115)	28.5% (86)	63% (29)
Pulmonary and upper respiratory	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0.9% (3)	1.0% (3)	0% (0)

*337 patients with body weight >40-80kg and 10 patients with body weight >80kg (81 to 100kg)

The Artequin dosage strength with a mefloquine total dose above 18.75 mg/kg has been selected as representative for the high mefloquine dose formulation (mean total mefloquine dose of 25 mg/kg) recently also recommended for Africa and defined as dose for the FDC of Artequin Paediatric. Therefore, the data thus defined allow best a comparison of incidences of AEs within the different relevant dosage groups.

The data presented in table 6 show the same tendency in children as demonstrated with the evaluation of table 5, i.e., no real dose-dependency of the gastrointestinal symptoms can be derived from the distribution of the events between the groups of children with a BW of 10 – 20 kg and those with a BW of >20 – 40 kg. Regarding the neurological and psychiatric events, a higher incidence in the group of children with higher body-weight has been show again. The same considerations regarding higher likelihood of reporting unwanted effects experienced during the therapy with increasing age can be applied.

The newly defined body-weight ranges, e.g., >20 to 40 kg for Artequin 300/750 are at the lower end slightly below the previously defined range of 25 to 35 kg in children. Therefore, children with a BW of about 20 kg actually receive a slightly increased total dose regarding mefloquine as combination partner in Artequin. Nevertheless, in none of the groups in the post-marketing studies treated with different doses of mefloquine was any relevant safety issue to be recorded thus demonstrating, that the doses as proposed in the new dosage concept are equally well tolerated to ensure high compliance with the therapy by both patient and prescribing physician.

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In none of the post-marketing studies were any clinically significant safety issues reported. These studies confirm the results of both phase III studies as well as those out of Study AM-P 001-2005 with Artequin Paediatric/Artequin 300/750 regarding good tolerability of Artequin in both paediatric and adult populations. Thus, Artequin Paediatric demonstrates a favourable safety profile with some trends to even better tolerability in its respective target population of small children (10 to 20 kg BW) as compared to patients with higher body-weights.

Since there is no interaction between artesunate and mefloquine when orally administered together, for precautions and warnings the relevant guidance on the use of the mono-substances apply as described in the relevant SmPC of Artequin Paediatric.

2.5.6 Benefits and Risks Conclusions

Global assessment of efficacy

A considerable number of clinical studies have evaluated and confirmed the excellent efficacy of the artesunate-mefloquine combination regimen in uncomplicated malaria. These promising findings led Mepha to the development of the Artequin concept with pre-packed combination-blisters of the already marketed artesunate and mefloquine tablets for one course of a three-day therapy.

The two randomized, double blind, parallel group, comparative, phase III studies investigating three different solid oral dosage strengths of Artequin (600/1500, 600/750 and 300/750) have proven in adults and children with uncomplicated malaria the high efficacy and adequate tolerability of this combination product.

The series of post-marketing Artequin studies conducted in different malaria endemic regions of Africa confirm the high efficacy of the Artequin therapy concept also in an extended therapeutic range for children below a body-weight of 30 kg and for adults of more than 55 kg. The overall experience out of these Artequin studies strengthened the decision to continue the clinical development plan of Artequin with the final goal to provide a fixed-dose combination of artesunate/mefloquine based on a pellet formulation for both active substances, and to further extend the dose range to small children not able to swallow tablets.

Several pharmacokinetic and in-vitro investigations build the basis for a successful dose-linear downscaling of the high mefloquine dose formulation of Artequin Co-blister to the first real galenical formulation for small children, namely Artequin Paediatric Stickpack. Following findings and conclusions out of these investigations are of importance:

- ▶ Bioequivalence demonstrated between the mefloquine tablet formulation of Artequin and the reference product Lariam allows to conclude on similarity between the two formulations regarding efficacy and safety.
- ▶ Lack of clinically relevant pharmacological interaction between the two active ingredients artesunate and mefloquine allows to take for reference the huge clinical experience with the single substances in the dose designed for the FDC of Artequin Paediatric Stickpacks (daily doses of artesunate 50 mg and mefloquine 125 mg). As a consequence, PK characteristics of both artesunate and mefloquine are supposed to be basically identical when administered alone or in combination. Therefore, the special clinical properties of the two antimalarials (fast but short acting artesunate – long lasting additive and protective effect of mefloquine) which are important for the ACT concept as used in the FDC Artequin Paediatric, are fully maintained in the combination.
- ▶ The proven linear dose dependency and proportionality of the pharmacokinetics of artesunate in the dose range of 50 to 200 mg and the known dose-linearity of mefloquine up to a dose of 1000 mg is an important prerequisite for down-scaling the artesunate/mefloquine combination from the already marketed dosage forms of Artequin 600/1500 and 300/750 in dose-linear proportionality to Artequin

Paediatric, i.e., to further halve the dose to the total therapeutic dose of 150 mg artesunate and 375 mg mefloquine.

- ▶ Similarity between the in-vitro dissolution profiles of the artesunate as well as mefloquine pellets in Artequin Paediatric and of the artesunate and mefloquine tablets in Artequin Co-blister demonstrate pharmaceutical equivalence of the two formulations. As a consequence, similar release of the active ingredients in the gastrointestinal tract, and thus, similar absorption patterns can be expected resulting in similar pharmacokinetic and pharmacodynamic characteristics of both the Artequin Co-blister dosage forms and the FDC of Artequin Paediatric.

Study AM-P 001-2005, carried out on children with acute uncomplicated *P. falciparum* malaria in Gabon provides a formal prove that the galenical dose-linearity realised in the dosage of Artequin Paediatric results in similar PK characteristics in children with a body weight of 10 to 20 kg as reached with the double dose, i.e., with Artequin 300/750 given to children with body-weight >20 to 40 kg. As consequentially expected, the study outcome showed an appropriate efficacy of Artequin Paediatric Stickpacks and Artequin 300/750 co-blisters as measured by 28-day and 14-day cure rates of 100% with rapid parasite and fever clearance, in their respective target population. These high healing rates were in line with those demonstrated in the other clinical studies (all post-marketing phase IV as well as the randomized, comparative phase III studies). Irrespective of the dose administered with regard of the mefloquine partner drug of Artequin, there were never issues regarding the efficacy of the therapy over the whole dose-range investigated.

Acceptability of intake of study medication is of great importance in pediatric patient populations as a prerequisite for compliance. Acceptability in the total paediatric study group kept constant above 80% over all three days of therapy which also demonstrate that no negative experience was linked to the drug administration, neither with tablets from Artequin 300/750 nor with the pellet formulation of Artequin Paediatric. Acceptability in the last group (BW 10 – 20 kg) was slightly lower most probably due to the lower age in this group often associated with more difficulties in medication intake in general.

Global assessment of safety

Overall, a reasonable safety profile has been reported in clinical studies with artesunate and mefloquine combination regimens. The relationship to study medication is rarely defined with certainty since similar symptoms as reported also rely to the malaria disease itself. For instance, the most commonly reported adverse effects were gastrointestinal disorders like abdominal pain, nausea, vomiting and diarrhoea, all of which are characteristic of acute malaria. Reported nervous system disorders like headache, dizziness and insomnia are, on the other hand, well know mefloquine-related side effects, and therefore, not unexpected in the combination therapy with artesunate/mefloquine. The likelihood of underreporting of AEs in small children has previously been discussed and should be taken into consideration while discussing incidences of AEs.

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The safety observations in the set of clinical studies with Artequin were of particular interest, since tolerability of the regimen is a crucial determinant for compliance. The overall safety profile of Artequin was adequate and clinically acceptable irrespective of patient age and reflected the well-known profiles of both drugs when used as monotherapy. The evaluation of the safety data out of the post-marketing Artequin studies with special focus on the paediatric population revealed no dose-dependency of the incidence of AEs within the group of small children with a BW between 10 to 20 kg, i.e., the target population for Artequin Paediatric. Thus, small children apparently tolerate the high dose Artequin therapy (as defined by the mean total mefloquine dose of 25 mg/kg) equally well, as demonstrated by the low incidence of gastrointestinal and neurological/psychiatric symptoms. No new clinically significant adverse reactions nor severe AEs have been observed with Artequin in the whole set of post-marketing studies.

The good tolerability of Artequin Paediatric in small children with acute uncomplicated *P falciparum* malaria was confirmed in Study AM-P 001-2005. Most of the observed changes in laboratory tests and vital signs were likely to reflect the recovery from the malarial disease rather than safety problems related to the study treatment. Many reported signs and symptoms were likewise due to intercurrent metazoan parasite infections, a situation not to be neglected in malaria endemic regions. As in the other Artequin studies described before, no severe nor serious Adverse Events related to the study medications have been reported in Study AM-P 001-2005.

The advantageous safety profile of Artequin in the whole paediatric population investigated has to be highlighted considering the fact that both study medications, i.e., Artequin 300/750 and Artequin Paediatric, contain the higher mean total mefloquine dosage of 25 mg/kg as currently recommended by the WHO for both Asia and Africa.

Overall conclusion

Based on the pharmacokinetic, in-vitro and clinical data it can be concluded, that down-scaling from Artequin 300/750 to the dose-linear FDC of Artequin Paediatric as a line-extension has successfully been realized. Artequin Paediatric is, with a mean total therapeutic dose of 12 mg/kg artesunate and 25 mg/kg mefloquine each, the first real FDC of the Artequin product range suitable for small children suffering from acute uncomplicated *P. falciparum* malaria. With a reasonable and known safety profile, Artequin Paediatric achieves the high clinical efficacy expected for this ACT of artesunate/mefloquine.

Artequin Paediatric can be administered without reservations to small children in their respective target group of 10 to 20 kg of body-weight and can be recommended as a safe and effective drug within the group of first-line ACTs for marketing authorisation in all endemic regions where malaria is a real threat to small children. This recommendation especially includes Africa from where the most clinical data and positive experiences from practice come from.

Post-marketing monitoring for possible development of resistance and further surveillance of the safety and efficacy of Artequin Paediatric in different African malarial endemic regions has to be advocated.

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Appendix I Summary of clinical trials with artesunate in combination with mefloquine in the treatment of uncomplicated *falciparum* malaria

Reference	Initial mean parasitemia count (per mm ³ blood)	Mean age in years (range)	No. of evaluable patients	Dosage regimen	Follow-up (days)	Mean clearance time (h)		No. of Response rate (%)	No. of patients with Recrudescence (%)
						fever	parasitaemia		

Non Comparative Trials Asia									
Looareesuwan et al. 1992 ⁵⁵ (Thailand)	NA	25.2 (18-43)	24	AS 600mg PO over 5d (100mg initially followed then 50mg q12h for 5d) + MQ 1250mg 12h after last AS dose	28	32.8	40.0	24 (100)	0
Looareesuwan et al. 1993 ⁵⁶ (Thailand)	17 741 ^a	25.8 (16-46)	48	AS 300mg PO over 2.5d (100mg initially followed then 50mg q12h for 2d) + MQ 750mg 12h after last AS dose	28	38.1	37.8	43 (90)	5 (10)
Wilairatana et al. 1998 ⁵⁷ (Thailand)	9 030 ^a	26.6 (15-60)	130	AS 600mg PO over 2d (200mg initially followed by 200mg at 12h and 24h) + MQ 1250mg q12h starting with first AS dose	28	42.5	46.4	126 (97)	4 (3)

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Reference	Initial mean parasitemia count (per mm ³ blood)	Mean age in years (range)	No. of evaluable patients	Dosage regimen	Follow-up (days)	Mean clearance time (h)		No. of Response rate (%)	No. of patients with Recrudescence (%)
						fever	parasitaemia		

Dose/Regimen-finding Trials Asia									
Looareesuwan et al. 1996 ⁵⁸ (Thailand)	38 018 ^a	25.2 (16-48)	58	AS 800mg PO over 1d (400mg q12h) + MQ 1250mg 12h after last AS dose (750mg initially followed by 500mg 12h apart)	28	55.3	41.6	49 (84)	9 (15.5)
	20 663 ^a	23.6 (16-44)	38	AS 800mg PO over 2d (200mg q12h) + MQ 1250mg 12h after last AS dose (750mg initially followed by 500mg 12h apart)	28	39.8	36.1	38 (100)	0
Sabchareon et al. 1998 ⁵⁹ (Thailand)	16 660 ^a	8.8	21	AS PO 6mg/kg/d for 3d + MQ 25mg/kg (15mg/kg on d2 and 10mg/kg 12h apart)	28	42.1	35.2	21 (100)	0

Reference	Initial mean parasitemia count (per mm ³ blood)	Mean age in years (range)	No. of evaluable patients	Dosage regimen	Follow-up (days)	Mean clearance time (h)		No. of Response rate (%)	No. of patients with Recrudescence (%)
						fever	parasitaemia		

Comparative Trials With Mefloquine Alone									
Looareesuwan et al. 1994 ⁶⁰ (Thailand)	22 919	25.9 (16-55)	50	AS 800mg Po over 2d (200mg q12h) + MQ 750mg single dose 6h after last AS dose	28	46.1	37.9***	46 (92)	4 (8)
	17 045	25.3 (16-51)	57	MQ 1250mg (750mg initially followed by 500mg 6h apart)	28	52.1	65.9	42 (74)	11 (19)
Nosten et al. 1994 ⁶¹ (Thailand) Study I	2810 ^a	16 (0.5-84)	124	AS 4mg/kg PO single dose + MQ 25mg/kg single dose concomitantly	28	48 ^b	26.4 ^c	103(83)	NA
	3549 ^a	17 (1.2-88)	115	MQ 25mg/kg single dose	28	79.2 ^{b*}	36 ^{c***}	90(78)	NA
Study II	5549 ^a	13 (0.5-58)	108	AS 10mg/kg PO (4mg/kg initially then 2mg/kg/d for 3d) + MQ 25mg single 24 h after first AS dose	63	38 ^b	28.8 ^c	100(98)	NA
	5731 ^a	12 (0.4-58)	129	MQ 25mg/kg single dose	63	79.2 ^{b***}	62.4 ^{c***}	64(56)	NA

Reference	Initial mean parasitemia count (per mm ³ blood)	Mean age in years (range)	No. of evaluable patients	Dosage regimen	Follow-up (days)	Mean clearance time (h)		No. of Response rate (%)	No. of patients with Recrudescence (%)
						fever	parasitaemia		
Karbwanng et al. 1994 ⁴² (Thailand)	31 091	(17-48)	12	AS 200mg single dose PO + MQ 1250mg 6h after last AS dose (750mg □initially followed by 500mg 6h apart)	42	31.2	47.5	8 (66)	4 (34)
	20 893	(19-40)	8	MQ 1250mg (750mg □initially followed by 500mg 6h apart)	42	44.7	82.3**	6 (75)	2 (25)

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Reference	Initial mean parasitemia count (per mm ³ blood)	Mean age in years (range)	No. of evaluable patients	Dosage regimen	Follow-up (days)	Mean clearance time (h)		No. of Response rate (%)	No. of patients with Recrudescence (%)
						fever	parasitaemia		

Comparative Trials With Artesunate Alone									
Karbwan et al .1996 ⁶² (Thailand)	32 000 ^a	24 (15-51)	28	AS 300mg PO (200mg initially followed by 100mg 12h later) + MQ 750mg 12h after last AS dose	42	24.3	37.1	22 (78.6)	6 (21.4)
	49 052 ^a	26 (15-58)	31	AS 700mg PO over 5d (300mg on d1 followed by 100mg on d2 to d5)	28	30.7	36.3	29 (93.6)	1 (3.2)

Footnotes, abbreviations and symbols: ^a Geometric mean parasite count; ^b Value represents the 90th percentile; ^c Value represents the 50th percentile; ^d Median

* indicates $p < 0.05$, compared with other treatment regimen; ** indicates $p < 0.01$, compared with other treatment regimen; *** indicates $p < 0.002$, compared with other treatment regimen.

AS: artesunate; ARTE: artemisinin; AM: artemether; MQ: mefloquine; QNN: quinine; TC: tetracycline; SP: sulfadoxine/pyrimethamine
PO: orally; PR: intrarectally; IV: intravenously; IM: intramuscularly; d: day(s); h: hour(s); qxh: administered every x hours;