APPLICATION FOR INCLUSION OF ARTESUNATE /AMODIAQUINE FIXED DOSE COMBINATION FOR PEDIATRIC TABLETS IN THE WHO ESSENTIAL DRUG LIST

1. Summary statement of the proposal for inclusion

Malaria is an important cause of death and illness in children and adults in tropical countries.
P. falciparum is responsible for virtually all of the estimated 700,000 to 2.7 million deaths per year that occur predominantly (75%) in African children [(1)].

The WHO recommends combinations of antimalarials for the treatment of *P.falciparum* uncomplicated malaria, to counter the threat of resistance of *P.falciparum* to monotherapies, and to improve the treatment outcome [(9)].

Artemisinin-based combination therapies (ACTs) are now generally considered as the best current treatment for uncomplicated *P.falciparum* malaria [(9)] and are more and more widely used. As of April 2006 (data provided by WHO/GMP) 60 countries have adopted and 33 are implementing ACTs worldwide. In Africa, 15 countries have adopted AS+AQ as first line treatment (Burundi*, Cameroon, Côte d'Ivoire, Democratic Republic of Congo, Gabon*, Ghana*, Guinea, Liberia, Madagascar, Mali, Senegal*, Sao Tomé & Principe*, Sierra Leone*, Sudan (South)* and Zanzibar* - implemented by countries with *). Elsewhere, Indonesia has also adopted AS+AQ.

We propose that the artesunate/amodiaquine fixed dose combination tablets (doses of 25mg/67.5 mg, 50mg/135 mg and 100mg/270 mg artesunate/amodiaquine respectively) be registered in the WHO essential drug list as a fixed dose combination therapy for the treatment of uncomplicated *P. falciparum* malaria, especially in paediatric patients.

The development of this drug was initiated by the FACT project (Fixed dose Artesunate Combination Therapy) that began in 2002 under the umbrella of Médecins Sans Frontières (and then the non-profit product development organisation DNDi) in coordination with TDR (the UNICEF-UNDP-World Bank-WHO's Special Programme for Research and Training in Tropical Diseases). The objective of the FACT project was to develop a fixed dose combination of artesunate-amodiaquine that would improve patient compliance and would be made available to all countries with low rates of resistance to amodiaquine. In 2004, Sanofi-Aventis teamed up with the FACT partners to bring its expertise in industrial, preclinical and clinical development, to optimize the quality of the drug and to expedite its availability.

Rationale on the proposed formulation:

1- The artesunate/amodiaquine fixed dose combination was formulated to ensure that patients take both drugs together in the right dose, with a particular attention paid to paediatric needs (dose ratio, age-adapted strengths, optimized pharmaceutical form…). The WHO considers patient adherence to treatment as a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision, and that co-formulation is probably a very important contributor to adherence [(14)]. As mentioned in the WHO guideline for registration of fixed dose combination medicinal products[(14)], the development of fixed dose combinations is becoming

increasingly important from a public health perspective, for an optimal treatment of malaria and for the prevention of drug resistance. Fixed dose combinations simplify treatment regimens, improve patient adherence and facilitate the implementation of interventional programs.

2- There are currently no paediatric artesunate-containing drug products or paediatric artesunate-containing combined therapies listed in the WHO essential drug list [(2)] for uncomplicated malaria.

3- The only fixed dose combined therapy listed in the WHO essential drug list is an artemether/lumefantrine combined therapy (20mg /100mg) that is not recommended in children below 10 kg [(2)]. The proposed artesunate/ amodiaquine fixed dose combination tablets can be used in children weighing 4.5 kg and over.

4- The artesunate/amodiaquine fixed dose combination was developed to provide to all patients with doses as close as possible to 4 mg/kg/day and 10 mg/kg/day for artesunate and amodiaquine, respectively [(3)]. Dosing recommendations were made for four consecutive body weight and age ranges that are predicted to result in the lowest possible proportion of over or under dosing.

5- The artesunate/amodiaquine fixed dose combination was developed to reduce the number of tablets that should be administered per day: one artesunate/amodiaquine tablet per day is recommended for children between 4.5kg and 36 kg. Three different dosages depending on body weight and age ranges are available as shown in the table below.

Body weight ranges (age ranges)	Co-blistered tablets of artesunate and amodiaquine	**Fixed dose combination artesunate / amodiaquine bilayer tablet**	artemether lumefantrine combination tablet
≥4.5kg to < 9 kg (2 to 11 months)	½ tablet of amodiaquine ½ tablet of artesunate per day for 3 days	**1 tablet (25mg artesunate/67.5 mg amodiaquine) per day for 3 days**	Not recommended
≥9kg to <18kg (1 to 5 years)	**1** tablet of amodiaquine **1** tablet of artesunate per day for 3 days	**1 tablet (50mg artesunate/135 mg amodiaquine) per day for 3 days**	Between 10kg-15kg 6 tablets over 3 days Between 15-18 kg 12 tablets over 3 days
≥18kg to <36kg (6 to 13 years)	**2** tablets of amodiaquine **2** tablets of artesunate per day for 3 days	**1 tablet (100mg artesunate/270 mg amodiaquine) per day for 3 days**	Between 18-25 kg 12 tablets over 3 days Between 25-35 kg 18 tablets over 3 days
≥ 36kg (14 years and above)	**4** tablets of amodiaquine **4** tablets of artesunate per day for 3 days	**2 tablets (100mg artesunate/270 mg amodiaquine) per day for 3 days**	Above 35 kg 24 tablets over 3 days

6- The artesunate/amodiaquine fixed dose combination is formulated and packaged to guaranty the stability of the active ingredient even under tropical conditions. Packaged in aluminium/aluminium blisters, the current shelf-life of the tablets is 24 months. Stability tests are on-going with the objective of documenting a 36 months shelf-life.

Rationale on the proposed dosage form:

Liquid formulations are considered as the most appropriate formulations for younger children (below 8 years of age) if the dose volume, the palatability and the stability are satisfactory. As artesunate is not stable in solution, a reconstituted liquid formulation stable for 3 days under tropical conditions could not be envisioned.

However, based on the criteria of the EMEA/CHMP/PEG/194810/2005 guideline "Formulations of choice for the paediatric population" [(4)], the artesunate / amodiaquine solid oral dosage forms (tablets) present several features of interest:

- for the paediatric population under 6 years :
  - Tablets can be dissolved in water before administration. They can be considered as soluble tablets because they disintegrate in water in less than 3 minutes in accordance with the European Pharmacopoeia,
  - Tablets can also be crushed and administered with liquid or semi-liquid food.

- for the paediatric population over 6 years:
  - no particular issue was documented regarding the acceptability by children of the taste, smell or texture of the tablets,
  - feedback from clinical investigators did not evidence any issue for administration to children whatever their age. The fixed dose combination is very easy to administer in children because only one daily tablet is needed,
  - the tablets are small: 10 mm diameter for toddlers and 13 mm for children. They can be easily swallowed, or they can be dissolved, crushed and administered with liquid or semi-liquid food.

- for the paediatric population in general:
  - Children are unlikely to tolerate repeated administration of medicines which are uncomfortable, painful or stressful. The present tablets allow a dose regimen and mode of administration in accordance with this aim,
  - a simple dosage regimen [once a day dosing facilitating patients' compliance and therefore diminishing risks of treatment failure and development of parasite resistance],
  - there are no excipients such as preservatives, sweeteners, fillers, solvents, colouring agents or coating material that should cause adverse effects in children,
  - knowing how bodyweight cannot always be easily assessed in field conditions, this drug can be prescribed based on either body weight or on age.

- for the parent/caregiver, ease, convenience and reliability of administration, through:
  - convenient presentations: a single Alu/alu blister of 3 tablets (one tablet once a day for three days up to13 years of age (35kg)) or a single Alu/alu blister of 6 tablets (2 tablets once a day for three days from 14 years of age (36kg and above)),
  - better stability, accuracy of dosing and improved portability over liquid formulations,
  - minimal dosage frequency,
  - one dosage form fits the full range of paediatric patients.

- for procurement and distribution:
    - Solid dosage forms such as fixed dose combinations facilitate the logistics of procurement and distribution compared to liquid forms (in terms of weight/volume) or to loose combinations (in terms of quantities).

- Packaged in Alu/Alu blisters the product is stable up to 24 months. Stability studies are ongoing until 36 months.

Proof of efficacy and safety:

Amodiaquine is listed in Essential Medicines WHO model list (revised March 2005) and should preferably be used as part of combination therapy. Artesunate is listed in the complementary list.

The clinical efficacy and safety of the artesunate amodiaquine combination is supported in the registration file by **14 studies**. **Five studies** were performed with **a theoretical 2.5 artesunate/amodiaquine dose ratio** based on monotherapy and weight adjusted posology (free combination amodiaquine 10mg/kg/day and artesunate 4 mg/kg/day), **8** other **studies** with **a 3.1 dose ratio based on age adjusted posology (co-blister)**, and the last one with the optimized dose ratio 2.7 (fixed dose combination).
Another study with a 2.7 ratio was performed after submission of the regulatory dossier.

The table below details the number of patients exposed to the three artesunate-amodiaquine dose ratios.

Extent of exposure

Weight adjusted posology	**Coarsucam™**	**Age adjusted posology**
Dose ratio 2.5	**Dose ratio** **2.7**	Dose ratio 3.1
5 safety and efficacy studies	2 efficacy and safety study	8 safety and efficacy studies
N= 2,710	N=971	N=1,464

The doses of artesunate and amodiaquine for the fixed dose combination were selected based on a study recently published in the WHO Bulletin. Demographic data of over **88,000 African children and adults**, including malaria patients, were used to select 4 different presentations based on age and weight. The artesunate/amodiaquine doses that were selected are expected to provide the lowest possible risks of over- and under-dosage.

The efficacy and safety of the fixed dose combination was confirmed in a study performed in Burkina Faso. A 3 days treatment of the fixed dose combination was evaluated in a randomised, controlled, open-label, parallel-group study, versus a loose combination (AS+AQ= Arsumax® + Flavoquine®) of the individual drugs, in children with malaria attack due to *P. falciparum*. The primary study objective was to show the non-inferiority in terms of efficacy of the fixed combination amodiaquine/artesunate (AS/AQ) compared to both drugs given as a loose combination (AS+AQ). For this study, a total of 750 children with an age range from 6 months up to 5 years inclusive, with body weight of at least 5 kg were included.
For the primary analysis PCR-corrected parasitological cure rates at Day 28 were similar in both treatment groups in all datasets. The upper bound of the 90% confidence interval for the difference in PCR-corrected parasitological cure rates (AS+AQ-AS/AQ) was always <0.05, thus demonstrating the non inferiority of AS/AQ compared to AS+AQ. Analysis of PCR-corrected parasitological cure rates at Day 28 in the mPP dataset provides an assessment of the treatment efficacy when it is actually taken. In this dataset, efficacy rates of both the tested drugs are above the limit fixed in the 2006 WHO recommendations for efficacy of new treatments (95%), namely 96.01% for AS+AQ and 95.74% for AS/AQ.

The incidence of general adverse events was consistent with what can be expected for young patients presenting with malaria. In particular, it is difficult to assign reports of fatigue, nausea, vomiting to the study drugs, the malaria infection itself or to concomitant conditions. Based on what is known of artesunate and amodiaquine safety profile, no unexpected adverse events occurred.

In addition, a multinational, randomised, single blind comparative Phase III trial was carried out in Cameroon, Madagascar, Mali, and Senegal, in order to assess the non inferiority of the fixed dose combination versus artemether/lumefantrine. A total of 941 patients, including 433 children under 5 years of age, weighing at least 10 kg, were included in the study between March and December 2006.
The study is completed and data analysis is currently ongoing.

Rationale on cost:

The pharmaceutical dosage form for paediatric patients is the same than the one for adults. The paediatric formulation is homothetic to the adult formulation and is manufactured with the same equipment. This ensures production and cost viability for these paediatric formulations.

This is the first fixed dose combination of artesunate and amodiaquine. On the public market, the only fixed dose combination which is comparable to artesunate/amodiaquine is artemether/lumefantrine.

Sanofi-Aventis has developed a program that makes drugs available through both the public and private distribution channels to reach all population segments:

- On the private market, the artesunate +amodiaquine fixed dose combination is intended to be available at a target price for children of less than 4 Euros per treatment.

- Public tenders prices fluctuate over time. However, based on the latest tender prices, artesunate/amodiaquine fixed dose combination can be estimated to be 50% cheaper than Coartem® at the present time. With a "no profit-no loss" approach, the treatment target price will be approximately 0.8 Euros for adults and 0.5 Euros for children.

Quality:

- Each active ingredient manufacturer is declared GMP compliant by the local authorities,
- Sanofi-Aventis' Maphar finished product manufacturing site is declared GMP compliant by the Moroccan authorities and was inspected by MSF on 30/31 January and 1st February 2007 and no critical findings were reported. Furthermore, a WHO GMP inspection is planned in June 2007.

2. Name of the focal point in WHO submitting or supporting the Application

3. Name of the organisation(s) consulted and/or supporting the Application

DNDi: Drug for Neglected Diseases Initiative
1, Place Saint Gervais
CH-1201 Genève-Switzerland

MSF: Médecins Sans Frontières
8, Rue Saint-Sabin- 75011 Paris-France

4. International Non-proprietary Name (INN, generic name) of the medicine

Artesunate /amodiaquine tablet is a fixed dose combination of two antimalarial drugs artesunate (INN) and amodiaquine (INN).

5. Dosage form or strength proposed for inclusion

5.1. Chemical characteristics

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide extracted from a plant used in traditional Chinese medicine, known as sweet or annual wormwood (Artemisia annua).
The chemical mechanism of action of artesunate has been widely studied and appears well established. The artesunate endoperoxyde's bridge is split by heme within the infected erythrocyte, generating singlet oxygen. Parasite proteins, particularly in membranous structures, are thus alkylated, leading to parasite death.

Amodiaquine is a synthetic amino 4-quinoline antimalarial. Its activity is characterized by a schizonticidal action on all *Plasmodium* species. Therefore it is used to treat acute illnesses by destroying intraerythrocytic forms.
The chemical mechanism of action of amino 4-quinoline derivatives against *Plasmodium* is not yet completely known. It is nonetheless accepted that these derivatives, one of which is amodiaquine, penetrate the infected red blood cells in a specific way and prevent the parasite from polymerizing heme into an insoluble product called hemozoin, leading to parasite death.

5.2. The formulation proposed for inclusion:

Artesunate (AS) plus amodiaquine (AQ) is one of the three WHO-recommended ACTs to treat uncomplicated *P. falciparum* malaria in Africa. Both Artesunate and Amodiaquine are part of the WHO List of Essential Medicines [(2)].

The artesunate/amodiaquine fixed dose combination was formulated to ensure that patients take both drugs together in the right dose, with a particular attention paid to paediatric needs (dose ratio, age-adapted strengths, optimized pharmaceutical form…). The WHO considers patient adherence to treatment is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision, and that co-formulation is probably a very important contributor to adherence [(14)]. As mentioned in the WHO guideline for registration of fixed dose combination medicinal products[(14)], the development of fixed dose combinations is becoming increasingly important from a public health perspective, for an optimal treatment of malaria and for the prevention of drug resistance. Fixed dose combinations simplify treatment regimens, improve patient adherence and facilitate the implementation of interventional programs.

The artesunate/amodiaquine fixed dose combination was developed to provide doses as close as possible to 4 mg/kg/day and 10 mg/kg/day for artesunate and amodiaquine respectively (WHO's recommendations, see also section 9.4).

The rationale for the selected artesunate and amodiaquine doses is based on study results recently published in the WHO Bulletin[3]. Demographic data of over 88,000 African children and adults, including malaria patients, were used to select 4 different presentations based on age and weight. The artesunate/amodiaquine doses that were selected are expected to provide the lowest possible risks of over- and under-dosage (see also section 9.4).

The artesunate/amodiaquine fixed dose combination was developed to reduce the number of tablets that should be administered per day: one artesunate/amodiaquine tablet per day is recommended for children between 4.5kg and 36 kg. Three different dosages depending on body weight and age ranges are available as shown in the table below.

Body weight range (age range)	Co-blistered tablets of artesunate and amodiaquine	**Fixed dose combination artesunate and amodiaquine bilayer tablet**	artemether lumefantrine combination tablets
≥4.5kg to < 9 kg (2 to 11 months)	**½** tablet of amodiaquine **½** tablet of artesunate per day for 3 days	**1 tablet** (25 mg artesunate/67.5 mg amodiaquine) **per day for 3 days**	Not recommended
≥9kg to <18kg (1 to 5 years)	**1** tablet of amodiaquine **1** tablet of artesunate per day for 3 days	**1 tablet** (50 mg artesunate/135 mg amodiaquine) **per day for 3 days**	Between 10kg-15kg 6 tablets over 3 days Between 15-18 kg 12 tablets over 3 days
≥18kg to <36kg (6 to 13 years)	**2** tablets of amodiaquine **2** tablets of artesunate per day for 3 days	**1 tablet** (100 mg artesunate/270 mg amodiaquine) **per day for 3 days**	Between 18-25 kg 12 tablets over 3 days Between 25-35 kg 18 tablets over 3 days
≥ 36kg (14 years and above)	**4** tablets of amodiaquine **4** tablets of artesunate per day for 3 days	**2 tablets** (100 mg artesunate/270 mg amodiaquine) **per day for 3 days**	Above 35 kg 24 tablets over 3 days

Artesunate/amodiaquine tablets are available as round bilayer tablets : one layer is yellow colored, the other one is white to slightly yellow, with score line, engraved on one side "AS" and on the other side "25", "50" or "100" depending of the concerned strength.

The tablets contain a fixed combination of the two active substances -artesunate and amodiaquine- with respective doses of 25, 50 and 100 mg for artesunate and 67.5, 135 and 270 mg for amodiaquine (base):
- 25mg/67.5 mg for treatment of children between 2 and 11 months of age (≥ 4.5 kg to < 9 kg),
- 50mg/135 mg for treatment of children between 1 and 5 years of age (≥ 9 kg to < 18 kg),
-100mg/270 mg for treatment of children (and adults) over 6 years of age (≥ 18 kg).

Liquid formulations are considered as the most appropriate formulation for younger children (below 8 years old) if the dose volume, the palatability and the stability are satisfactory. As artesunate is not stable in solution, it was not possible to consider a reconstituted liquid formulation of artesunate-amodiaquine that would be stable for 3 days under tropical conditions.

However, based on the EMEA/CHMP/PEG/194810/2005 guideline "Formulations of choice for the paediatric population" [(4)], the artesunate/amodiaquine solid oral dosage forms (tablets) present several features of interest:

- for the paediatric population under 6 years :
  - Tablets can be dissolved in water before administration. They can be considered as soluble tablets because they disintegrate in water in less than 3 minutes in accordance with the European Pharmacopoeia (see table below),
  - Tablets can also be crushed and administered with liquid or semi-liquid food.

Batch number	0001	0002	0002	0003	0005	0006
Strength artesunate/ amodiaquine	50/135mg	25/67.5mg	50/135mg	25/67.5mg	50/135mg	25/67.5mg
Disintegration time	58s	46s	40s	31s	41s	35s

- for the paediatric population over 6 years:
  - no particular issue was documented regarding the acceptability by children of the taste, smell or texture of the tablets,
  - feedback from clinical investigators did not evidence any issue for administration to children whatever their age. The fixed dose combination is very easy to administer in children because only one daily tablet is needed,
  - the tablets are small: 10 mm diameter for toddlers and 13 mm for children. They can be easily swallowed, or they can be dissolved, crushed and administered with liquid or semi-liquid food.

- for the paediatric population in general:
  - Children are unlikely to tolerate repeated administration of medicines which are uncomfortable, painful or stressful. The present tablets allow a dose regimen and mode of administration in accordance with this aim,
  - a simple dosage regimen [once a day dosing facilitating patients' compliance and therefore diminishing risks of treatment failure and development of parasite resistance],
  - there are no excipients such as preservatives, sweeteners, fillers, solvents, colouring agents or coating material that should cause adverse effects in children.

- for the parent/caregiver, ease, convenience and reliability of administration, through:
  - convenient presentations: a single Alu/alu blister of 3 tablets (one tablet once a day for three days up to13 years of age (35kg)) or a single Alu/alu blister of 6 tablets (2 tablets once a day for three days from 14 years of age (36kg and above)),
  - better stability, accuracy of dosing and improved portability over liquid formulations,
  - minimal dosage frequency,
  - one dosage form fits the full range of paediatric patients,
  - knowing how bodyweight cannot always be easily assessed in field conditions, this drug can be prescribed based on either body weight or on age.

- for procurement and distribution:
  - Solid dosage forms such as fixed dose combinations facilitate the logistics of procurement and distribution compared to liquid forms (in terms of weight/volume) or to loose combinations (in terms of quantities).

5.3. Stability of the formulation

The Sanofi-Aventis artesunate/amodiaquine fixed dose combination is formulated and packaged to guaranty the stability of the active ingredients even under tropical conditions. Packaged in aluminium/aluminium blisters, the current shelf-life of the tablets is 24 months. Stability studies are on-going with the objective of documenting 36 months stability. The manufacturer recommends that the drug is stored below 30°C in the original package [(5)].

6. International availability – sources, if possible manufacturers

6.1. Sources and manufacturers

The fixed dose combination of artesunate/amodiaquine is manufactured by Sanofi-Aventis Pharma in its manufacturing plant: MAPHAR Laboratories, km 7, Route de Rabat-Aïn Sebaâ Casablanca, Morocco.

Maphar Laboratories has the capacity to produce the three dosage strengths according to Good Manufacturing Practice (GMP) and in sufficient quantities to meet expected needs. It has been declared GMP compliant by the Moroccan authorities. Furthermore it was inspected by MSF on 30/31 January and 1st February 2007 and no critical findings have been reported.
A WHO GMP inspection is planned in June 2007.

Amodiaquine is manufactured at:
IPCA Laboratories Limited
89 A-B, 90-91
Industrial Estate, Pologround
Indore
India

or by

IPCA Laboratories Limited
Sejavta
Ratlam, Pin: 457 002
India

Artesunate is manufactured at:
KNOLL/ABBOTT LIESTAL LTD
Oristalstrasse 65
4410 Liestal
Switzerland

Each active ingredient manufacturer is certified as GMP compliant by their local authorities.

As there is no patent covering this artesunate/amodiaquine fixed dose combination, the reference Marketing Authorization will enable third parties to submit applications for generic versions of this product.

6.2. History of the product

In January 2006, "*the WHO requested pharmaceutical companies to end the marketing and sale of "single-drug" artemisinin malaria medicines, in order to prevent malaria parasites from developing resistance to this drug. The use of single-drug artemisinin treatment – or monotherapy- hastens development of resistance by weakening but not killing the parasite. When used correctly in combination with other antimalarial drugs in artemisinin Combination Therapies (ACTs), artemisinin is nearly 95% effective in curing malaria and the parasite is highly unlikely to become drug resistant. ACTs are currently the most effective medicine available to treat malaria.(…)Additionally, to anticipate and prevent the onset and spread of drug resistance in the long term, WHO urges the global malaria research community and the pharmaceutical industry to rapidly invest in the design of the next generation of antimalarial drugs* [(6)].

Sanofi-Aventis has, for several years, undertaken an active policy of ACT development, based on artesunate and on amodiaquine, that, in combination, are an ACT, which consists, as recommended by the WHO, in the simultaneous administration of at least two blood antimalarial drugs, with independent modes of action and different intraparasitic biochemical targets.

Sanofi-Aventis registered initially Arsucam®, a co-blister presentation, containing both artesunate and amodiaquine tablets.
Arsucam® has been marketed since approximately two years by Sanofi-Aventis in sub-Saharan Africa.

Compliance to treatment is essential to ensure treatment effectiveness and to prevent future resistance to ACT. But when combinations are provided as two separate drugs, there is a risk that patients take only one of the two drugs or fail to complete the whole course. Taking one drug without the other increases the risk of failure and development of resistance. Fixed dose combinations combine two drugs into one tablet, instead of separate tablets, to ensure that the patients take both drugs together in the right dose. The WHO considers that patient adherence is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision, and that co-formulation is probably a very important contributor to adherence [(1)]. From a public health perspective, an important approach to addressing the management of malaria has included the development of fixed dose combination of individual components administered together in one dosage form. Fixed dose combinations simplify treatment regimens, improves patient adherence and facilitates the implementation of interventional programs.

Based on these recommendations, work was undertaken by sanofi aventis to develop a fixed dose combination of artesunate and amodiaquine, with optimised tablet strengths designed to maximize the proportion of patients, and in particular young children, predicted to receive appropriate doses of amodiaquine and artesunate, based on their bodyweight.

In parallel, work on a similar approach was also initiated by the FACT project (Fixed dose Artesunate Combination Therapy) that began in 2002 under the umbrella of Médecins Sans Frontières (and then the non-profit product development organisation DNDi) in coordination with TDR (the UNICEF-UNDP-World Bank-WHO's Special Programme for Research and Training in Tropical Diseases). The objective of the FACT project was to develop a fixed dose combination of artesunate-amodiaquine that would improve patient compliance and would be made available to all countries with low rates of resistance to amodiaquine. In 2004, Sanofi-Aventis teamed up with the FACT partners to bring its expertise in industrial, preclinical and clinical development, to optimize the quality of the drug and to expedite its availability.

6.3. International availability and production capacity

Effective malaria treatments are often not accessible to those who need it, because of their price, inappropriate distribution channels or lack of information. Sanofi aventis has developed a comprehensive program, called Impact Malaria that aims at mobilizing the expertise and resources of a major pharmaceutical manufacturer against malaria.

To support the pharmaceutical development and the industrial manufacture of the fixed dose combination, sanofi aventis chose its manufacturing site in Morocco, in accordance with its "Access to Medicines" policy to manufacture in the "South" products for the "South", so as to help local employment and favour technology transfers. This site has well-developed industrial equipment, with a high level of technology, thanks to a major investment program, that began in 2000 and allowed the plant to reach appropriate quality levels required for the development of international projects.

To allow the manufacture of the fixed dose combination, the registration file was first submitted in Morocco on December 7, 2005 and the Marketing/Manufacturing Authorisation was granted on February 1, 2007.
Following this initial registration, several endemic countries have then granted local Marketing Authorisation.
These countries are: Benin, Burkina Faso, Congo, Côte d'Ivoire, Gabon, Guinea, Kenya, Madagascar, Mali, Mauritania, Democratic Republic of Congo, Togo and Zanzibar.
Registration procedures are ongoing in a certain number of other African countries: Burundi, Cameroun, Ghana, Niger, Nigeria, Senegal, Tanzania, Chad and Uganda.

In parallel, on February 23, 2007, Sanofi-Aventis submitted the fixed dose combination dossier to the World Health Organisation, as part of the pre-qualification registration program concerning Artemisinin based antimalarial products.
The dossier is under examination by the WHO assessors.

The current maximal production capacity is of 3 millions tablets per month (all strengths) equivalent to 36 millions tablets per year (l2 millions blisters per year).
Dependent on the quantities needed the product can be scaled up to 25 million blisters per year (the acquisition of a subsidiary packaging line would be then necessary).
There is no restriction on the availability of the raw materials artesunate and amodiaquine.

7. Whether listing is requested as an individual medicine or as an example of a group

Artesunate/amodiaquine fixed dose combination tablets are proposed to be listed in the WHO essential drug list [2] within the pharmacotherapeutic group "antimalarial medicines for curative treatment", subdivision 6.5.3 antimalarial medicines – curative treatments.
In this group, the only combination therapy listed in the March 2005 revision is artemether + lumefantrine (20mg/120 mg) combination tablets which are not recommended for a use in children below 10 kg. Thus there is currently no recommended antimalarial treatment in the WHO essential drug list for children below 10 kg.

The Sanofi-Aventis artesunate/amodiaquine fixed dose combination can be prescribed to children with bodyweight as low as 4.5kg, and only requires one artesunate/amodiaquine tablet per day for children between 4.5kg and 36 kg. Importantly, knowing how bodyweight cannot always be easily assessed in field conditions, this drug can be prescribed based on either body weight or on age. The table below compares dosing regimens for the artesunate-amodiaquine co-blister and fixed dose presentations to the artemether-lumefantrine fixed dose combination.

Body weight range (age range)	Co-blistered tablets of artesunate and amodiaquine	**Fixed dose combination artesunate and amodiaquine bilayer tablet**	artemether lumefantrine combination tablet
≥4.5kg to < 9 kg (2 to 11 months)	½ tablet of amodiaquine ½ tablet of artesunate per day for 3 days	**1 tablet** (25 mg artesunate/67.5 mg amodiaquine) **per day for 3 days**	Not recommended
≥9kg to <18kg (1 to 5 years)	**1** tablet of amodiaquine **1** tablet of artesunate per day for 3 days	**1 tablet** (50 mg artesunate/135 mg amodiaquine) **per day for 3 days**	Between 10kg-15kg 6 tablets over 3 days Between 15-18 kg 12 tablets over 3 days
≥18kg to <36kg (6 to 13 years)	**2** tablets of amodiaquine **2** tablets of artesunate per day for 3 days	**1 tablet** (100 mg artesunate/270 mg amodiaquine) **per day for 3 days**	Between 18-25 kg 12 tablets over 3 days Between 25-35 kg 18 tablets over 3 days
≥ 36kg (14 years and above)	**4** tablets of amodiaquine **4** tablets of artesunate per day for 3 days	**2 tablets** (100 mg artesunate/270 mg amodiaquine) **per day for 3 days**	Above 35 kg 24 tablets over 3 days

The artesunate/amodiaquine fixed dose combination simplifies treatment regimens, can improve patient adherence and can facilitate the implementation of interventional programs.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Malaria is an important cause of death and illness in children and adults in tropical countries. Mortality currently estimated at over a million people per year, has risen in recent years, probably due to increasing resistance to antimalarial medicines[9]. *P. falciparum* is responsible for virtually all of the estimated 700,000 to 2.7 million deaths per year that occur predominantly (75%) in African children [1]. The World Health Organization (WHO) has decreed that prompt and effective treatment is a key element of a successful strategy to control malaria.

In recent years, Chinese scientists isolated a very potent and effective anti-malarial drug out of the plant *Artemisia Annua*, known as artemisin. Artemisin and its derivatives are very potent and effective anti-malarial drugs (Heemskerk W et al, 2006 [7]; Krishna S, 2004 [8] and WHO, 2006 [9]) and for patients with *P.falciparum* malaria resistant to the common antimalarial drugs, the use of artesmisin and its derivatives is essential (WHO, 2000b [10]; 2001a, b [11] [12]).
The importance of artemisinin and its derivatives was recognised by the WHO Expert Committee on Essential Drugs (WHO 2000a [13]). Artemisinins were first available as monotherapy. However, monotherapy must be adhered to for at least five days, but often seven days.
In practice, adherence to these relatively long treatment regimens is low. This behaviour may result in treatment failures in the development of resistances.

As a result, the WHO recommended recently the use of artemisinin-based Combination Therapies (ACT). ACT have several distinct advantages in that: (1) they produce rapid clinical and parasitological cure; (2) there is as yet no documented parasite resistance to them and resistance to the combinations is most unlikely to occur; (3) they reduce gametocyte carrier rates and (4) there are generally well-tolerated (Heemskerk W et al, 2006 [7]; Krishna S, 2004 [8] and WHO 2001a [11] and 2006[9]). At present, only the ad hoc combinations of artesunate with mefloquine (MQ), amodiaquine (AQ), chloroquine (CQ) or sulfadoxine-pyrimethamine (SP) were widely used operationally in areas of multidrug resistant *P. falciparum* malaria. However, fixed dose combinations of artemisinin derivatives should have operational advantages since they should be easier to use will provide greater compliance in the target populations than ad hoc combinations (WHO, 2001a and b [11] [12]).

CURRENT USE AND RATIONALE OF THE FIXED DOSE COMBINATION

DEVELOPMENT

The WHO recommends combinations of antimalarials for the treatment of *P. falciparum* uncomplicated malaria, to counter the threat of resistance of *P. falciparum* to monotherapies, and to improve treatment outcome [(14)]. The WHO actively encourages malaria-endemic countries to adopt Artemisinin-based combination therapy (ACT), and many of them are starting to do so. As of April 2006 (data provided by WHO/GMP) 60 countries have adopted and 33 are implementing ACT worldwide. In Africa, 15 countries have adopted artesunate and amodiaquine as first line treatment (Burundi*, Cameroon, Côte d'Ivoire, Democratic Republic of Congo, Gabon*, Ghana*, Guinea, Liberia, Madagascar, Mali, Senegal*, Sao Tomé & Principe*, Sierra Leone*, Sudan (South)* and Zanzibar* - implemented by countries with *). Elsewhere, Indonesia has also adopted artesunate and amodiaquine.

The artesunate-amodiaquine fixed dose combination is an ACT, which consists, as recommended by the WHO, in the simultaneous administration of two blood antimalarial drugs; artesunate and amodiaquine with independent modes of action and different intraparasitic biochemical targets.

Both artesunate and amodiaquine are already registered and available on the market of endemic countries for this indication and are frequently and widely used in the clinic, individually and in combination with each other and with other compounds.
Artesunate has been marketed in Africa for 10 years and in Asia for 15 years and can be considered as an active substance with a well-established use in endemic countries.
Amodiaquine has been on the market for about 60 years and can be considered as an active substance with a well-established use.
Amodiaquine is listed in Essential Medicines WHO model list (revised March 2005) and should preferably be used as part of combination therapy. Artesunate is listed in the complementary list.

The drugs used in combination should theoretically have similar pharmacokinetics and pharmacodynamics, no adverse pharmacological interaction, and no additional toxicity. With the current artemisinin based combinations, the pharmacology characteristics are different in that the artesunate acts quickly and has a very short half-life, and the companion drugs act more slowly but have longer half-lives. The latter ensures that the companion drugs act for long enough to kill the remaining parasites and those parasites are never exposed to artesunate alone. In this way, artesunate is protected.

Compliance to treatment is essential to ensure treatment effectiveness and to prevent future resistance to ACT. But when combinations are provided as two separate drugs, there is a risk that patients take only one of the two drugs or fail to complete the whole course. Taking one drug without the other increases the risk of failure and development of resistance. Fixed dose combinations combine two drugs into one tablet, instead of separate tablets, to ensure that the patients take both drugs together in the right dose. The WHO considers that patient adherence is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision, and that co-formulation is probably a very important contributor to adherence [(14)].

As mentioned in the WHO guideline for registration of fixed dose combination medicinal products[14], the development of fixed dose combinations is becoming increasingly important from a public health perspective. Fixed dose combination simplifies treatment regimens, improves patient adherence and facilitates the implementation of interventional programs.

TARGET POPULATION AND RATIONALE ON THE RATIO/DOSE

Three artesunate amodiaquine dose ratios were tested in clinical trial and two of them are already widely used:
-a theoretical 2.5 dose ratio, based on monotherapy and **weight adjusted posology**. It could be obtained by using free combination of amodiaquine 10mg/kg/day and artesunate 4 mg/kg/day,
-a 3.1 dose ratio, based on **age adjusted posology**. It could be obtained by using marketed artesunate amodiaquine co-blister,
-the optimized dose ratio 2.7, that could be obtained by the proposed fixed dose combination. The rationale of the selected doses of ASAQ is based on study results recently published in the WHO Bulletin. Demographic data of over 88,000 African children and adults, including malaria patients, were used to select 4 different presentations based on age and weight. These artesunate/ amodiaquine doses, that can be prescribed based on **either body weight or on age**, are expected to provide the lowest possible risks of over- and under-dosage.

The target population is linked to the indication: *treatment of uncomplicated Malaria attacks due to P. falciparum strains, which are susceptible to the product*.

9. Treatment details

9.1. Method of administration

Oral route
Tablets should be swallowed with a drink of water.
For administration to the youngest children (below 6 years old), the tablets can be dissolved in water or crushed and administered with liquid or semi-liquid food.

9.2. Dosage

Theoretical dosage of artesunate and amodiaquine is adjusted to body weight as follows: 4 mg/kg of artesunate and 10 mg/kg of amodiaquine base once daily for 3 days. However, artesunate / amodiaquine fixed dose combination dosage may be prescribed according to either age or body weight ranges according to the following prescription table, resulting in actual dosing ranges between 2 and 10 mg/kg for artesunate and 7.5 and 15 mg/kg for amodiaquine:

Weight range (approximate age range)	**Product**	**1st day of treatment**	**2nd day of treatment**	**3rd day of treatment**
≥4.5kg to < 9 kg (2 to 11 months)	25mg/67.5mg blister of 3 tablets	1 tablet	1 tablet	1 tablet
≥9kg to <18kg (1 to 5 years)	50mg/135mg blister of 3 tablets	1 tablet	1 tablet	1 tablet
≥18kg to <36kg (6 to 13 years)	100mg/270mg blister of 3 tablets	1 tablet	1 tablet	1 tablet
≥ 36kg (14 years and above)	100mg/270mg blister of 6 tablets	2 tablets	2 tablets	2 tablets

9.3. Duration

The daily dose must be repeated during 3 consecutive days.

9.4. WHO treatment guidelines

WHO's 2006 treatment guidelines on the use of artesunate/amodiaquine [9] state that the total recommended treatment is 4 mg/kg base weight of artesunate and 10 mg/kg base weight of amodiaquine given once a day for 3 days corresponding to an amodiaquine/artesunate ratio dose of 2.5.

The currently available treatment of artesunate/amodiaquine combination is presented as separated scored tablets containing 50 mg of artesunate (i.e. Arsumax®) and 153 mg of amodiaquine base (i.e. Flavoquine®) and as co-blister (i.e. Arsucam®).

Thus, up to now, the WHO recommended regimen for all patients and in all situations is therefore as follows:

Age	**Dose in mg (Number of tablets)**					
	Artesunate (50 mg)			**Amodiaquine (153 mg)**		
	Day 1	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**
5-11 months	25 (1/2)	25	25	76 (1/2)	76	76
≥ 1-6 years	50 (1)	50	50	153 (1)	153	153
≥ 7-13 years	100 (2)	100	100	306 (2)	306	306
> 13 years	200 (4)	200	200	612 (4)	612	612

The rationale of the selected 2.7 dose ratio of artesunate and amodiaquine in the fixed dose combination is based on study results recently published in the WHO Bulletin [3].

Weight-based dosing in malaria endemic countries is challenging because functioning weighing scales are scarce and access to formal health services is limited. Thus, the majority of malaria treatments are dosed based on the patient's age. Cognisant of this practice, the WHO has both age and weight-based recommendations for the commonly used antimalarial drugs. However age/weight correlation is usually based on non-African population data.

The optimised tablet strength and blister design for an age-based dosing regimen of artesunate/amodiaquine as a fixed dose combination have been determined, using a novel approach by modeling currently available, relevant, weight-for-age data from malaria endemic African countries [3]. This dataset is referred to as malaria weighted anthropometric reference (MWAR) dataset (88000 African children and adults).
This methodology allows the design of practical regimens that maximize the proportions of patients receiving acceptable drug doses that should be safe and efficacious.
The strategy of simplicity over dose accuracy demanded a definition of acceptable dosing ranges for both drugs. The dosing range for artesunate was wide (5 fold, 2 to 10 mg/kg), reflecting its tolerability and, therefore, wider therapeutic index. There was less flexibility with amodiaquine (2 fold, 7.5 to 15 mg/kg). Thus, amodiaquine determined the final dosing and age categories.
The convention of doubling the drug dose per age category and selected five age groups which had an approximate doubling in median bodyweight was followed: (1) 0-1 months (4.2 kg), (2) 2-11 months (6.9 kg), (3) 1-6 years (13.3 kg), (4) 7-13 years (25.6 kg), and (5) ≥ 14 years (58.0 kg).

The model predicted that virtually all patients in each age category would receive a therapeutic dose of artesunate. Tablets containing 25 and 100 mg were chosen because this dose gave the lowest risk of overdosing; 1 in 10,000 patients would receive more than 10 mg/kg/day and 1 in 1000 patients less than 2 mg/kg/day. The same rationale applied to the choice of the amodiaquine dosage (67.5 and 270 mg). The higher degree of under dosing associated with the 67.5 and 270mg tablets was considered less critical because the profound parasiticidal effect of artesunate reduces substantially the parasite biomass leaving a small number of parasites to be killed by the amodiaquine. With this tablet strength, just over 83% of patients were predicted to receive a therapeutic dose of amodiaquine, a reasonable figure.

The convention of selected five age groups which had an approximate doubling in median bodyweight in this database, eventually conducted to change the age range; children 6 years old have to be treated with tablets containing 270 mg of amodiaquine instead of 153 mg amodiaquine with the coadministration treatment.

10. Summary of comparative effectiveness in a variety of clinical settings

The clinical efficacy and safety of the artesunate/amodiaquine combination is supported in the registration file by **14 studies**:
- **Five studies** were performed with **a theoretical artesunate: amodiaquine dose ratio of 2.5** based on monotherapy and weight adjusted posology (free combination amodiaquine 10mg/kg/day and artesunate 4 mg/kg/day),
- **Eight** other **studies** with **a 3.1 dose ratio based on age adjusted posology (co-blister)**, and,
- **One study of the fixed dose combination** with the optimized **2.7 dose ratio**.

In addition, **another study** with the artesunate/amodiaquine fixed dose combination at the **2.7 dose ratio** was performed after submission of the regulatory dossier and is currently being analyzed.

The table below details the number of patients exposed to the three artesunate-amodiaquine dose ratios.

Extent of exposure

Weight adjusted posology	**Coarsucam™**	**Age adjusted posology**
Dose ratio 2.5	**Dose ratio** **2.7**	Dose ratio 3.1
5 safety and efficacy studies	2 efficacy and safety study	8 safety and efficacy studies
N= 2,710	N=971	N=1,464

Co-administration of both artesunate and amodiaquine presented independently

The development of artesunate/amodiaquine co-administration was based on the results of studies initiated within the framework of the WHO/TDR antimalarial program whereby the efficacy and safety of several combinations of the artemisinin derivative artesunate (AS) with chloroquine (CQ), amodiaquine (AQ), sulfadoxine- pyrimethamine (SP) and mefloquine (MQ) were assessed [15].

The effective dose regimen of the AS+AQ combination was established through a clinical program established as follow:

- WHO/TDR Studies (ratio dose = 2.5)

3 randomized, double-blind studies **conducted in children** with uncomplicated *P.falciparum* malaria in 3 African countries; Senegal, Gabon and Kenya, (representing different forms of malaria transmission and patterns of drug resistance but where amodiaquine was expected to be efficacious [16]) as part of the WHO/TDR program. These 3 studies, which are referred to as WHO/TDR studies n° 1, 2 and 3, compared the efficacy and safety of the artesunate (AS) plus amodiaquine (AQ) combination (4 mg/kg/day of AS and 10 mg/kg/day of AQ for consecutive 3 days) to AQ (Camoquin TM) alone (10 mg/kg/day for 3 days) plus placebo (for double-blind conditions to be met). The AS+AQ combination was composed of Arsumax® and Camoquin™ and is therefore referred to as the Arsumax ®+ Camoquin™ combination.

Study n°1: was conducted in Senegal (Casamance region) where malaria transmission is seasonal (July-November) and the entomological inoculation rate is 25/person-year. Chloroquine resistance is high (50-68%), and AQ (30mg/kg total) has a 14-day parasitological efficacy of 61%.

Study n°2: was conducted in Gabon where a rate of Cloroquine resistance of 53% was recently reported [18]. In the Lambarene area, malaria transmission is hyperendemic and perennial and the entomological inoculation rate is 50/person-year. The 28-day AQ (25mg/kg total) parasitological efficacy was of 91% in 1994.

Study n°3: was conducted in southern Kenya (Entasopia and Migori) where malaria transmission is seasonal (May-July). The 14-day efficacy of AQ before the start of the study was 63% in Entasopia and 97% in Migori.

These 3 randomized double blind studies were carried out in **a total of 941 children** up to 10 years of age with body weight of **at least 5 kg**. All patients had uncomplicated malaria characterized by *P.falciparum* monoinfection with parasite counts ranging from at least 1000/µl to less than 250 000/µl and a history of fever during the past 24 hours. The demographic and pathological profile of the patients was well defined, and similar in the 3 studies, thus allowing assessing whether the efficacy of the drug regimen which was used (weight-adjusted Arsumax ®+ Camoquin™ versus Camoquin ™ + placebo) was reproducible in all 3 countries (Senegal, Gabon and Kenya).

The results convincingly demonstrated the superiority of the efficacy of Arsumax®+Camoquin™ over that of Camoquin™ alone in the treatment of uncomplicated *P. falciparum* malaria. Even though the parasitological response rates at Day 14 and Day 28 were not significantly different between groups in Senegal, response rates with the combination in this country were only a close second to those in Gabon as illustrated in Figure 1. The lack of difference between the 2 groups in the Mlomp area of Senegal may be due to the efficacy of AQ remaining high in this area. It must be noted that parasitemia decreased more quickly in the presence of Arsumax® in Senegal as well as in Gabon and Kenya. The most obvious beneficial effect of the adjunction of Arsumax® to Camoquin™ was seen in Kenya. However, response rate at Day 28 with the combination was only 68.3%, probably due to the low mean age of the studied children population (only 2.7 years) and the relative lack of acquired immunity in such a young population, or possibly because of a higher incidence of AQ resistance.

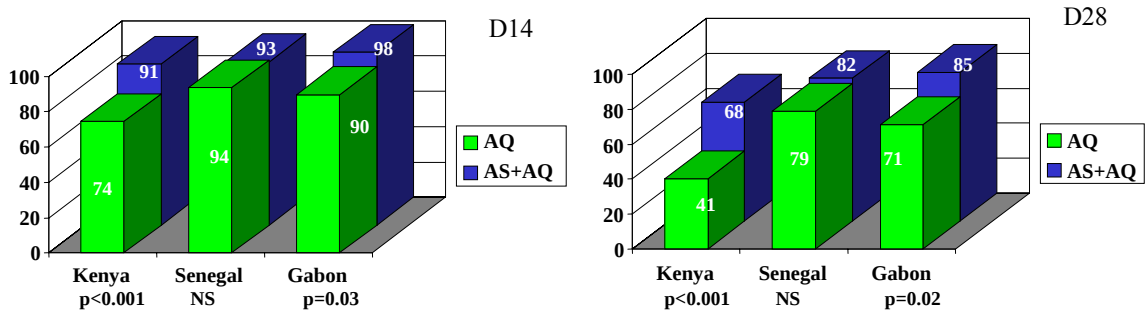


Figure 1 - PCR-Uncorrected Efficacy Response Rates in WHO/TDR Studies

Gametocyte carriage rose in the Camoquin™ group in all 3 countries. Compared with Camoquin™, Arsumax®+Camoquin™ reduced gametocyte carriage on Days 7, 14 and 21 in all 3 countries; the difference between groups was statistically significant on Day 7 and Day 14 in Kenya and of borderline significance on Day 14 in Senegal [Figure 2].

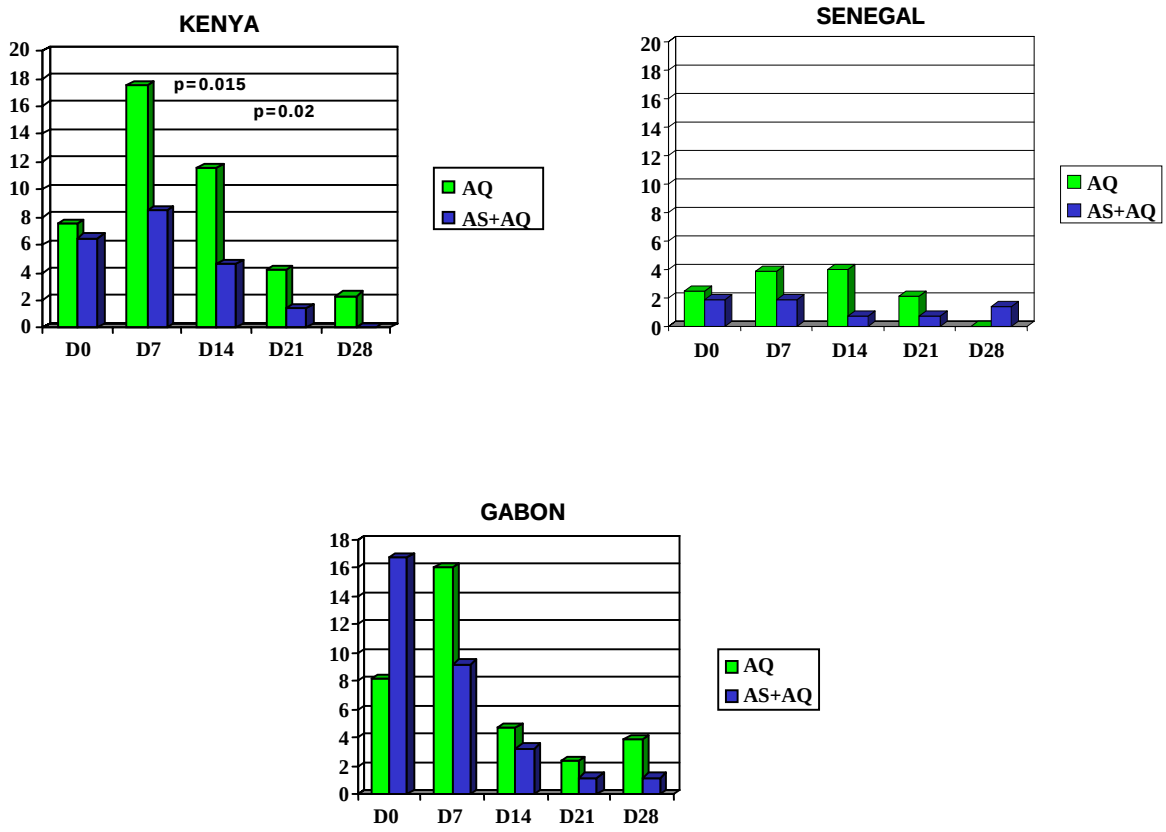


Figure 2 - Gametocyte Carrier Rate in WHO/TDR Studies

- Implementation study (ratio dose = 2.5):

Subsequently, the same Arsumax®+Camoquin™ drug regimen (4 mg/kg/day of AS and 10 mg/kg/day of AQ for 3 consecutive days) was used for 2 consecutive seasons in Senegal as first-line treatment of uncomplicated malaria in South-Western Senegal. Again, this combination proved highly effective in conditions resembling routine use.

In the implementation study conducted in Casamance (Senegal), the 624 patients treated over the 2 consecutive transmission seasons of Year 2000 and Year 2001 were recruited among a **mixed population of children and adults, although a majority of patients were children** as shown by mean ages, 11 years for year 2000 and 10 years for year 2001 (for the 253 Arsumax®-treated patients). All selected patients in this open-label implementation study had fever or history of fever and microscopically confirmed *P. falciparum* malaria. Thus, overall, they were included according to criteria similar to those of the patients of the WHO/TDR. This type of field study permitted to confirm the efficacy of the weight-adjusted Arsumax®+Camoquin™ treatment in less contingent conditions in a large number of patients over 2 seasons.

This open-label study with Arsumax®+Camoquin™ was carried out in Mlomp (Senegal) like the WHO/TDR Study No. 1. Although not meant to be a comparative study, it comprised a smaller group of patients treated with Camoquin™ alone. Efficacy rates at Day 28 during both seasons was similar in the 2 treatment groups, although slightly higher than in the WHO/TDR study: 95.8% with a 95% CI of [92.2; 98.1] and 94% [90.7; 96.4] during Years 2000 and 2001 for Arsumax®+Camoquin™, respectively, and 92.5% [81.8; 97.9] and 95.7% [85.5; 99.5] for Camoquin™ alone, respectively. These data confirm the lack of difference between the 2 groups and the good results of either treatment seen in that region of Senegal in the more rigorous methodological conditions of the WHO/TDR study.

- Artesunate/amodiaquine co-blister Phase III Studies (ratio dose = 3.1)

While the antimalarial efficacy of the Arsumax®+Camoquin™ combination had been clearly demonstrated, coprescribing separate marketed products, i.e., Arsumax® and Camoquin™ or Flavoquine® was economically unaffordable for the African Health Authorities and not practical to implement as such. The ARSUCAM® coblisters containing both AS and AQ tablets were developed to provide the antimalarial combination as a low-price, age-adjusted, easy-to-use dosage forms for children up to 6 years of age, children in the 7-13 years age range and for patients 14 years and over, respectively .
Eight Phase III studies were conducted with ARSUCAM® coblister. Among them, 6 studies were carried out in different regions of Senegal as part of the National Malaria Control Program (NMCP) [17]. They include:

- Study A, conducted in Bougoula Hameau in Mali (where a steady increase in the prevalence of *P. falciparum* resistance to chloroquine has been documented) was a randomized, blinded study comparing 3 treatments: ARSUCAM®, SP+Arsumax® and Arsumax® alone, conducted in a total of **752 patients** with **age ranging from 0.6 years to 38 years.**

Of those, 252 were treated with weight-adjusted ARSUCAM®. Inclusion criteria were similar to these described for the WHO/TDR patients, except that patients showing infection with *Plasmodium Specie* (not only those with *P. falciparum* infection) could be included. However, efficacy results are reported only for those with *P. falciparum* infection.

- Study B, conducted in Niakhar, Central Senegal where malaria transmission is markedly seasonal (July-December), was a randomized, single-blind study comparing 3 combinations: ARSUCAM®, SP+Arsumax® and SP+AQ, conducted in a total of **706** patients with age ranging **from 10 to 71 months** (i.e., approximately 1 to 6 years). Of those, 341 were treated with age-adjusted ARSUCAM®. Inclusion criteria were similar to those described for the WHO/TDR patients. This Phase 3 study mostly differs from the other Phase 3 studies on ARSUCAM® in that it was conducted in a rather large number of young children only.
- Open-label studies C and D of ARSUCAM® were conducted in two districts of Senegal, Guediawaye (where chloroquine resistance rate was 30% in 2002) and Podor (where periods of heavy transmission of malaria can be observed and where malaria is hypo-to-mesoendemic (inoculation rate of 5/person-year)).

- Study E, conducted in the Richard-Toll district (where chloroquine resistance rate was 40% in 2002) of Senegal, was a randomized, open-label study comparing the following 4 combinations: ARSUCAM®, Artequin® (AS+MQ), Coartem® (artemether+lumefantrine) 4 doses and SP+AQ.
- Study F, conducted in the Kaolack district (where malaria accounts for 45% of general morbidity and where chloroquine resistance rate reaches 42% in 2002) of Senegal, was a randomized, open- label study comparing the following 4 combinations: ARSUCAM®, Artequin® (AS+MQ), Coartem® (artemether+lumefantrine) 4 doses and SP+AQ.
- Study G, conducted in the Velingara district of Senegal (where chloroquine resistance was 27 % in 2002), was a randomized, open-label study comparing the following 4 combinations: ARSUCAM®, Artequin® (AS+MQ), Coartem® (artemether+lumefantrine) 4 doses and 6 doses, and SP+AQ.
- Study H, conducted in Comoros Union (where early treatment failure (ETF) with chloroquine reached 20% and accurate clinical and parasitological response (ACPR) was 60% in 2002 [i]), was a randomized, open-label study comparing the following 3 combinations: ARSUCAM®, AS+SP and CQ+SP.

Studies C, D, E, F, G and H were conducted in a total mixed population of 1136 children and adults among whom 462 were treated with age adjusted ARSUCAM®. Among the ARSUCAM® patients, **87 were aged 5 years or less**. Again, inclusion/exclusion criteria for these patients with uncomplicated *P. falciparum* monoinfection were similar to those used in the previously described studies.

Altogether, the baseline malarial characteristics of the patients of all clinical trials included in this application were similar: patients were all treated for uncomplicated malaria due to a monoinfection with *P. falciparum*, with counts of at least 1000/µL of blood, fever, mild-to-moderate anemia and no danger signs or severe malaria. Gametocytemia was not always specified, except for the 3 WHO/TDR studies and Study A. However, changes in the percentages of gametocyte carriers during a 28-day follow-up period were well described in the 3 WHO/TDR studies as well as in Studies A and B.

As presented in table below, efficacy results with ARSUCAM® in all Phase 3 studies were consistent with or even better than those obtained in the WHO/TDR studies with Arsumax®+Camoquin™.

Response Rates in Phase 3 Studies with ARSUCAM®

Study	A	B	C, D, E, F, G	H
Country	Mali	Senegal	Senegal	Comoros Union
Number of patients in ARSUCAM® group	237	341	360[a]	102
Primary efficacy endpoint	Clinical and parasitological efficacy at Day 28	Clinical and parasitological efficacy at Day 28	Clinical and parasitological efficacy at Day 28	Clinical and parasitological efficacy at Day 14
Results (uncorrected)	81.0%	ACPR (Day 28): 87.2%	ACPR (Day 28): 97.5%	ACPR (Day 14): 98.0%
Parasitological failure after PCR	1%	1.5%	PCR not available	1.0%

ACPR = accurate clinical and parasitological response; PCR = polymerase chain reaction
[a] all patients of the ARSUCAM® group in Studies C, D, E, F, G pooled

In Study A, the uncorrected response rate of 81% with ARSUCAM® was lower than that observed with the SP+AS bitherapy. However, after PCR correction, both bitherapies gave nearly complete (99.1%) or complete (100%) ACPR rate [figure 3]. The proportion of gametocyte carriers, of 6% at baseline decreased to less than 1% on Day 28 in the ARSUCAM® group. A similar pattern was seen in the other 2 groups. Fever decreased faster in the ARSUCAM® group compared to the SP+AS group and the AS5 group (5% febrile patients on Day 1 versus 9% and 13% in the SP+AS and AS5 groups, respectively; p <0.001), although it was nearly absent in all groups on Day 3.

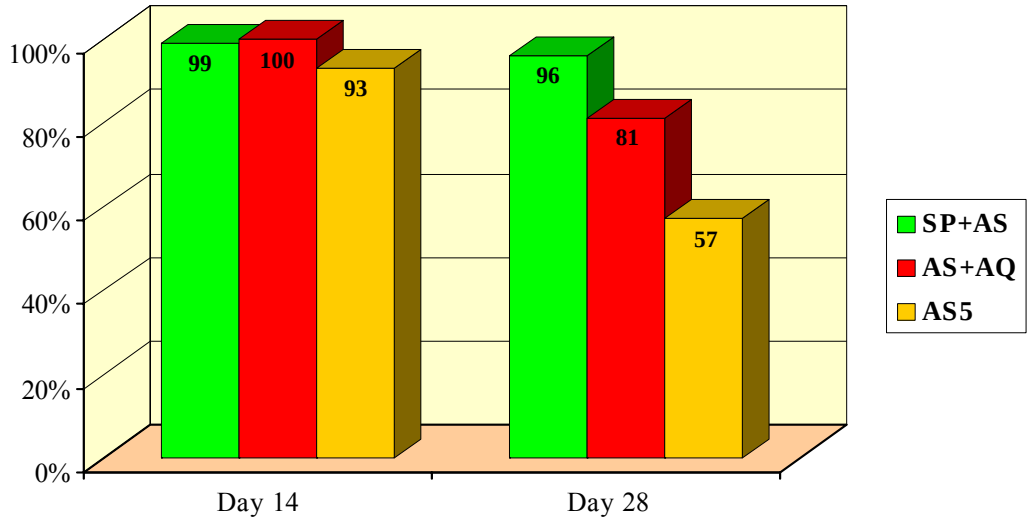


Figure 3 - Uncorrected Adequate Clinical and Parasitological Response Rate in Study A

The lower response rate in Study B is probably not clinically significant compared with results in the other studies. However, a polymerase chain reaction (PCR) check could be performed on 28 of the 36 patients with parasitemia on Day 28. As only 3 of the 28 patients for whom pair (Day 0 and Day 28) of PCR results were available, an extrapolated correction assessed the failure rate at 1.5%, which is a PCR-corrected response rate of 98.5%, similar to that in the other Phase 3 studies. Response rates on Day 28 with the comparators SP+AQ and SP+AS were 97.2% and 89.7%, respectively [figure 4], although no PCR correction was available for these groups. The proportion of gametocyte carriers was not significantly different between the 3 groups, but was consistently lower in the ARSUCAM® group on Days 7, 14 and 28.

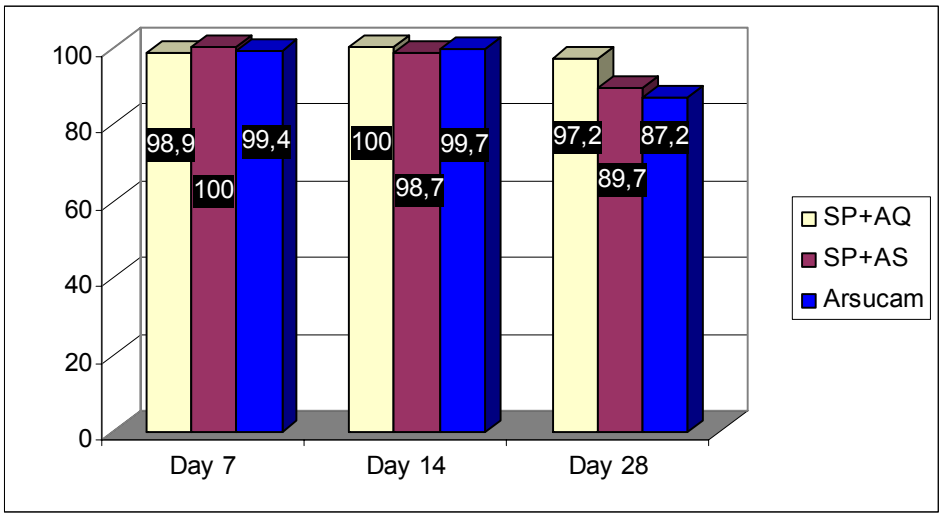


Figure 4 - Adequate Clinical and Parasitological Response Rates in Study B

Altogether, the data of Studies A and B demonstrate that ARSUCAM® is at least as effective as the SP+AQ or SP+AS bitherapy and more effective than Arsumax® alone for 5 days in children and adults.

In Studies C (district of Guediawaye), D (district of Podor), E (district of Richard-Toll), F (district of Kaolack), and G (district of Velingara) pooled together, ARSUCAM® (N = 360) provided, at Day 28, a response rate of 97.5% which was similar to the response rate with Artequin® (98.0%, N = 145), AQ+SP (98.8%, N = 161), Coartem® 4 doses (82.9%, N = 140) and Coartem® 6 doses (100%, N = 29) [see also figure 5]. Parasitological and fever clearances were rapid with percentages of febrile patients and parasite carriers of 1% and 5% at Day 2, respectively, and of 0% for both parameters at Day 3.

Parasitological clearance was also similar in all treatment groups, with 100% clearance obtained on Day 3. In Study C, the proportion of gametocyte carriers decreased steadily from 5.3% at Day 0 to 0% at Day 28, results consistent with those in WHO/TDR studies. In terms of response by study site, most of the failures (36/38, including 9 with ARSUCAM®) were reported in the district of Kaolack, and all failures but 1 were late treatment failures (LTF) occurred between Day 21 and Day 28. According to this author, some of the LTFs could be reinfections after Day 20. Kaolack is an important crossway between Gambia and Guinea, a fact that may increase transmission and the risk of reinfection.

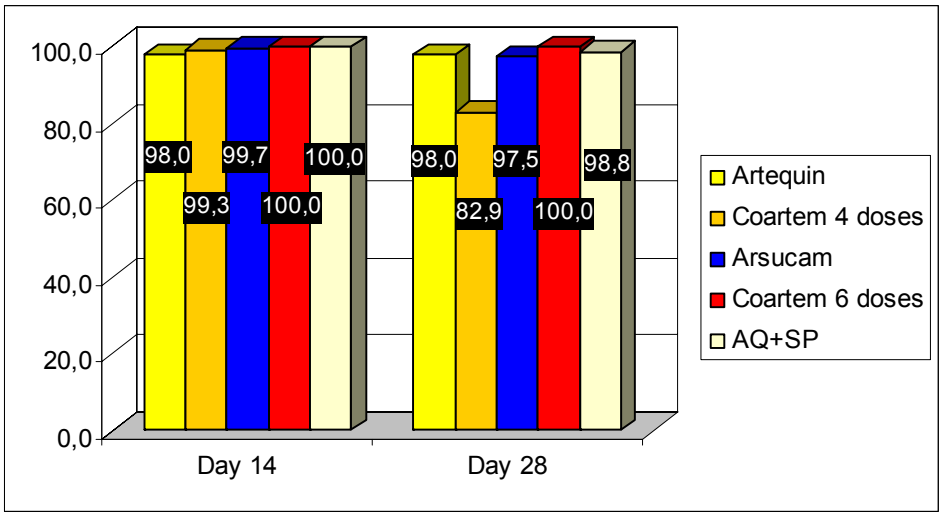


Figure 5 - Adequate Clinical and Parasitological Response Rates in Senegalese Studies C, D, E, F, G

Similarly consistent results were obtained in Study H carried out in the Comoros Union where efficacy response rate (ACPR rate) was 98% for ARSUCAM® (N = 102), 99% for AS+SP (N = 104) and 96% for CQ+SP (N = 95) [Figure 6].

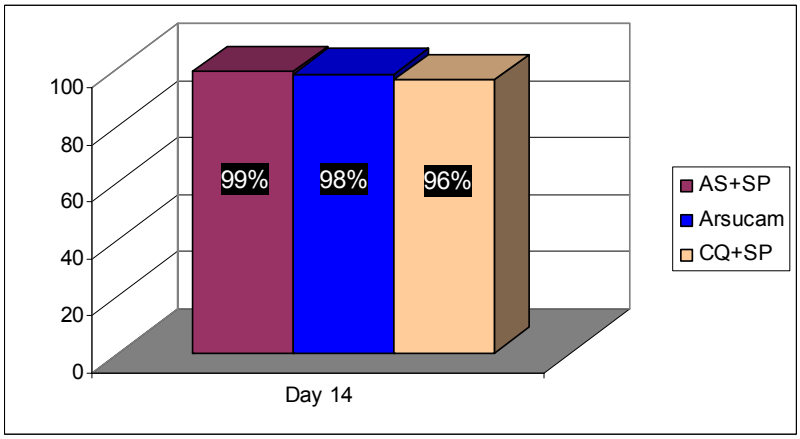


Figure 6 - Adequate Clinical and Parasitological Response Rates in Study H

WHO/TDR studies, as well as Study B with ARSUCAM®, were carried out in children population only. Results convincingly demonstrated (i) the superiority of the Arsumax®+Camoquin™ over Camoquin™ alone and (ii) the high response rate following ARSUCAM® (even before PCR correction). Other ARSUCAM® Phase 3 studies were carried out in a mixed population of patients (although mostly youngsters). **In studies A and H, however, separate analyses were reported for the whole population and for children aged 5 years or less**, i.e., in patients possibly more susceptible to infection because of a low level of immunity. In Study A, no difference was seen in efficacy rate on Day 14 between the lower age group (≤5 years) and the upper age group (>5 years). Likewise, in Study H, efficacy rate was similar in the <5-year-old group and in the whole study group (all ages combined). Altogether, the data demonstrate that the efficacy of artesunate amodiaquine combination covers all age groups.

No apparent clinically significant efficacy differences could be detected for the weight-adjusted Arsumax®+ Camoquin™ or the age-adjusted ARSUCAM® combinations across the countries (Senegal, Gabon, Kenya, Comoros Union) or across the Senegalese districts (Guediawaye, Podor, Richard-Toll, Kaolack, Velingara) where the clinical trials took place, even if failures (not PCR corrected) were seen in Kaolack district where the risk of reinfection may be specially high.

Efficacy of artesunate and amodiaquine presented as a fixed dose combination

To confirm the efficacy of a 2.7 AS:AQ dose ratio , a 3 days treatment of the fixed dose combination was evaluated in a randomised, controlled, open-label, parallel-group study, versus a loose combination (AS+AQ= Arsumax® + Flavoquine®) of the individual drugs, in children with malaria attack due to *P.falciparum*. This study was performed in Burkina-Faso, between October 8th 2004 and February 22th 2006, and sponsored by DNDi.
The primary objective was to show the non-inferiority in terms of efficacy of the fixed combination amodiaquine/artesunate (AS/AQ) compared to both drugs given as a loose combination (AS+AQ).
The secondary objectives were to evaluate treatment tolerability and safety:
- Clinical tolerability and safety measured by signs and symptoms which may appear after treatment and any Serious Adverse Events (SAEs),
- Biological tolerability and safety measured by biochemical and haematological parameters.

The study was carried out in a rural area located 120 km from Ouagadougou, where a high level of transmission can be observed during the rainy season (from July to December). In Burkina Faso, resistance to chloroquine has kept growing in the last 15 years. The rate of failure for chloroquine treatment was 24.5% in 1999, with parasitological failure at Day 28 for 70% of patients, and reached 62.9% and 81% at Day 14 and Day 28, respectively [19]. A study conducted in 2003 showed 70.8% of treatment failure with chloroquine (Sirima et al, unpublished data). No data relative to amodiaquine resistance level are available in this area.

For this study, a total of **750 children with an age range from 6 months up to 5 years inclusive**, with body weight of at least 5 kg were included. All patients had uncomplicated malaria characterized by *P. falciparum* monoinfection with parasite counts of at least 1000/µL and fever (uncorrected axillary temperature ≥ 37.5°C) at Day 0. Causes for exclusion were : signs of severe malaria, underlying diseases, allergy to drugs, intake of amodiaquine within 7 days prior to inclusion or intake of artemisin derivates within 3 days prior to inclusion, completed treatment with anti-malarial drugs within 7 days prior to inclusion (except chloroquine), and ongoing antibiotic treatment with drugs with anti-malarial activity (e.g. cotrimoxazole, tetracyclines, macrolides).

For the fixed dose combination treatments, tablets dosed with 25 mg of AS and 67.5 mg of AQ were used: one tablet a day for 3 days was administered to children up to eleven months of age, and 2 tablets a day for 3 days were given to children aged 1 to 5 years. For the loose combination, Arsumax® (50 mg AS) and Flavoquine® (153 mg AQ base) were used. This required for the youngest children (up to 11 month) the use of tablet fractions (half tablets) for both products, whereas older children were treated with one tablet of each product per day.

Four pre-planned datasets were used for analyses (detailed compositions of datasets are in Annexes 1 and 2)

- **The Intent-to-Treat (ITT)** dataset includes all patients randomised to treatment (750 patients). Patients were analysed according to the treatment they are randomly assigned to. All patients withdrawn from the study for any reason are considered as failure. The analysis of this dataset underestimates the efficacy of the tested drugs.
- **The Safety (SAF)** dataset includes all patients who received at least one dose of study medication (749 patients). This dataset is used for the safety evaluation.
- **The per-protocol (PP)** dataset includes all patients in the SAF dataset with no major protocol violations (682 patients).
- **The modified Per-Protocol (mPP)** dataset is a subset of the PP dataset whereby all patients that were withdrawn from the study, due to persistent inability to swallow the study drug or because drug-induced repeated vomiting within one hour of study drug administration, were removed (655 patients). The analysis of this dataset provides a closer evaluation of the treatment's efficacy when treatment is actually taken, and also of the *in vivo* susceptibility of parasites to the drug.

Primary endpoint

Since the ITT dataset stringently managed missing data as treatment failures, the event rate (cure rate) could be less than that on which the sample size was based and that could lead to a power less than 90%. For this reason, the PP dataset was the primary analysis dataset.

For the primary analysis PCR-corrected parasitological cure rates at D28 were similar in both treatment groups in all datasets. The upper bound of the 90% confidence interval for the difference in PCR-corrected parasitological cure rates (AS+AQ-AS/AQ) was always <0.05, thus demonstrating the non inferiority of AS/AQ compared to AS+AQ. Sensitivity analyses, planned in the Statistical Analysis Plan strongly support these results.

The analysis of the PP dataset provides an assessment of the treatment efficacy in the "per protocol" population defined in the study Statistical Analysis Plan. Efficacy rates were practically identical in both treatment groups: 92.06% for AS+AQ and 92.11% for AS/AQ (fixed dose combination). Of note, the PP population does not exclude patients that were withdrawn early on from the study, due to persistent inability to swallow study drug or because of drug-induced repeated vomiting within one hour of study drug administration.

Analysis of PCR-corrected parasitological cure rate at Day 28: PP dataset

Administered treatment (0=AS+AQ, 1=AS/AQ)		Cured? (PCR corrected)		Total
		No	Yes	
Artesunate+Amodiaquine	Frequency Row Pct	27 7.94	313 92.06	340
Artesunate/Amodiaquine	Frequency Row Pct	27 7.89	315 92.11	342
Total		54 7.92	628 92.08	682 100.00

Column 2 Risk Estimates						
	Risk	ASE	(Asymptotic) 90% Confidence Limits		(Exact) 90% Confidence Limits	
Total	0.9208	0.0103	0.9038	0.9378	0.9017	0.9372
Difference	-0.0005	0.0207	-0.0345	0.0335		

Analysis of PCR-corrected parasitological cure rates at D28 in the ITT dataset provides the most conservative assessment of efficacy rates that were practically identical in both treatment groups: 85.87% for AS+AQ and 85.33% for AS/AQ (Coarsucam™), as shown in the table below.

Analysis of PCR-corrected parasitological cure rate at Day 28: ITT dataset

Administered treatment (0=AS+AQ, 1=AS/AQ)		Cured? (PCR corrected)		Total
		No	Yes	
Artesunate+Amodiaquine	Frequency Row Pct	53 14.13	322 85.87	375
Artesunate/Amodiaquine	Frequency Row Pct	55 14.67	320 85.33	375
Total		108 14.40	642 85.60	750 100.00

Column 2 Risk Estimates						
	Risk	ASE	(Asymptotic) 90% Confidence Limits		(Exact) 90% Confidence Limits	
Total	0.8560	0.0128	0.8349	0.8771	0.8332	0.8767
Difference	0.0053	0.0256	-0.0368	0.0475		

Analysis of PCR-corrected parasitological cure rates at D28 in the mPP dataset provides an assessment of the treatment efficacy when it is actually taken. The mPP data set results from the exclusion of 27 children from the PP data set who did not take their initial treatment doses: 13 who spat out their treatment (5 in the AS/AQ group, 8 in the AS+AQ group) and 14 who experienced repeated vomiting (8 in the AS/AQ group, 6 in the AS+AQ group). In this dataset, efficacy rates of both the tested drugs are above the limit fixed in the 2006 WHO recommendations for efficacy of new treatments (95%), namely 96.01% for AS+AQ and 95.74% for AS/AQ (fixed dose combination), as shown in the table below.

Analysis of PCR-corrected parasitological cure rate at Day 28: mPP dataset

(Administered treatment (0=AS+AQ, 1=AS/AQ)		Cured? (PCR corrected)		Total
		No	Yes	
Artesunate+Amodiaquine	**Frequency** **Row Pct**	13 3.99	313 96.01	326
Artesunate/Amodiaquine	**Frequency** **Row Pct** **Col Pct**	14 4.26	315 95.74	329
Total		27 4.12	628 95.88	655 100.00

Column 2 Risk Estimates

	Risk	ASE	(Asymptotic) 90% Confidence Limits		(Exact) 90% Confidence Limits	
Total	0.9588	0.0078	0.9460	0.9716	0.9436	0.9707
Difference	0.0027	0.0155	-0.0229	0.0282		

Secondary endpoints

Non PCR-Corrected Parasitological Cure Rates at D28

As shown in the tables below, the non-inferiority of AS/AQ compared to AS+AQ is also demonstrated for the primary PP dataset (upper bound <0.05). Similar results were obtained in the mPP dataset.

Analysis of non PCR-corrected parasitological cure rate at Day 28: PP dataset

Administered treatment (0=AS+AQ, 1=AS/AQ)		Cured? (Non-PCR corrected)		Total
		No	Yes	
Artesunate+Amodiaquine	**Frequency** **Row Pct**	33 9.71	307 90.29	340
Artesunate/Amodiaquine	**Frequency** **Row Pct**	37 10.82	305 89.18	342
Total		70 10.26	612 89.74	682 100.00

Column 2 Risk Estimates						
	Risk	ASE	(Asymptotic) 90% Confidence Limits		(Exact) 90% Confidence Limits	
Total	0.8974	0.0116	0.8782	0.9165	0.8762	0.9159
Difference	0.0111	0.0232	-0.0271	**0.0493**		

Analysis of non PCR-corrected parasitological cure rate at Day28: mPP dataset

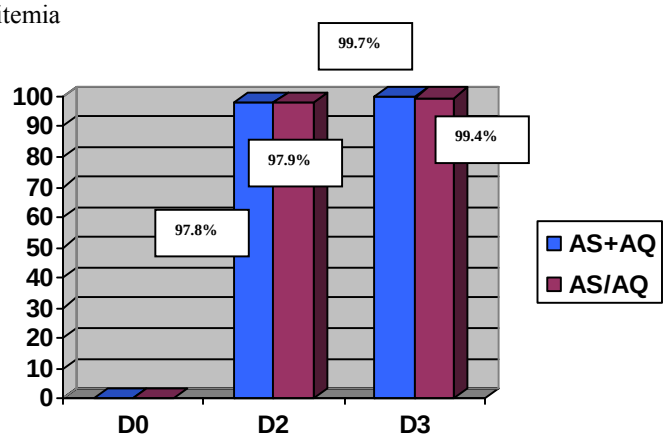
Administered treatment (0=AS+AQ, 1=AS/AQ)		Cured? (Non-PCR corrected)		Total
		No	Yes	
Artesunate+Amodiaquine	Frequency Row Pct	19 5.83	307 94.17	326
Artesunate/Amodiaquine	Frequency Row Pct Col Pct	24 7.29	305 92.71	329
Total		43 6.56	612 93.44	655 100.00

Column 2 Risk Estimates						
	Risk	ASE	(Asymptotic) 90% Confidence Limits		(Exact) 90% Confidence Limits	
Total	0.9344	0.0097	0.9184	0.9503	0.9162	0.9495
Difference	0.0147	0.0193	-0.0171	0.0465		

Proportions of Patients without Parasitaemia on D2 and D3: PP Dataset

A total of 633/647 (97.8%) patients had no parasitaemia on Day 2 and 639/642 (99.5%) patients had no parasitaemia on Day 3. Note that parasitaemia was not measured at D1. The parasitological clearance was similar in the 2 treatment groups. Similar results were obtained for the ITT and mPP datasets. The table below shows parasitaemia data on Days 2 and 3, in patients from the PP dataset.

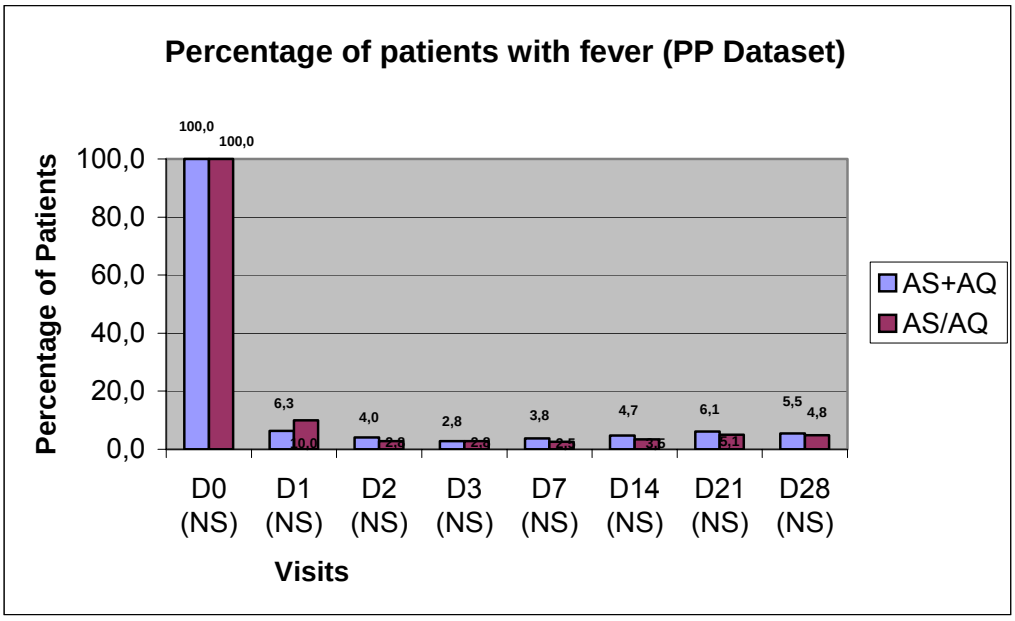
% of patients without parasitemia



Fever clearance:

A dramatic decrease of fever was rapidly achieved in both groups under treatment, without difference between the two groups. Similar results were obtained in the ITT and mPP datasets.

Number of patients with fever on Days 1, D 2and D 3: PP dataset

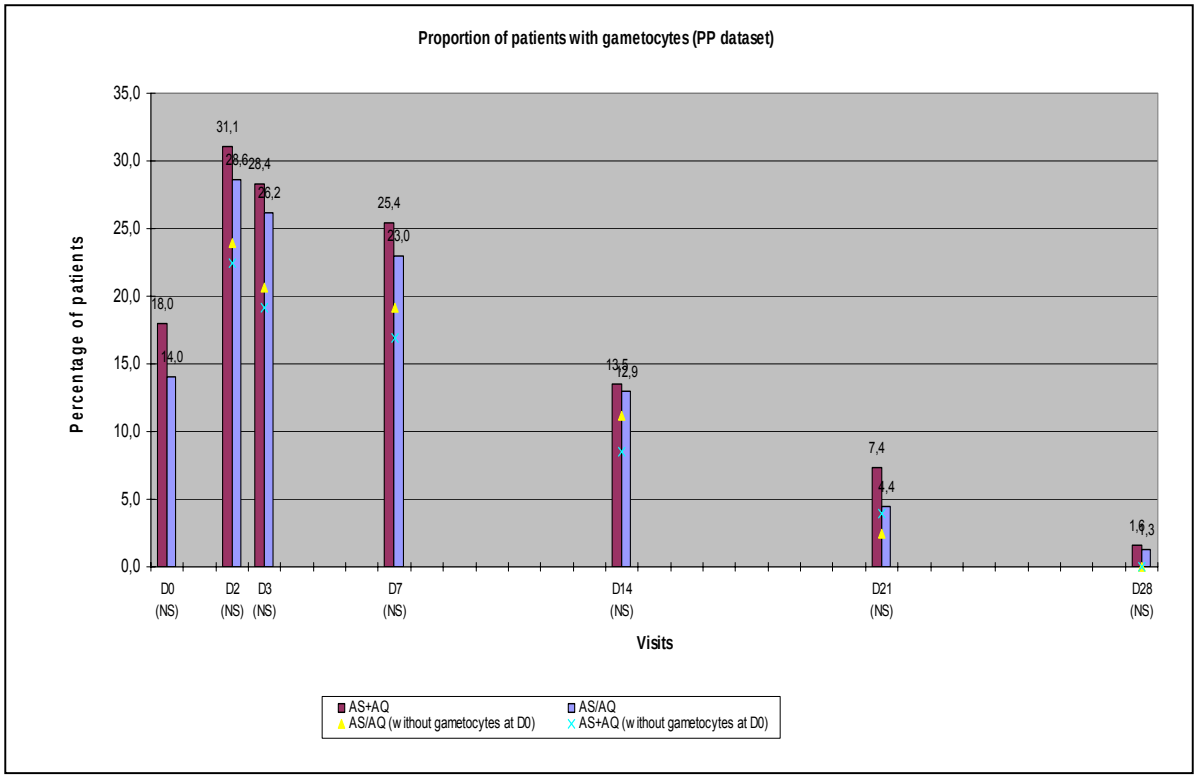


Proportion of patients with gametocytes at D0, D2, D3, D7, D14, D21 and D28: PP dataset

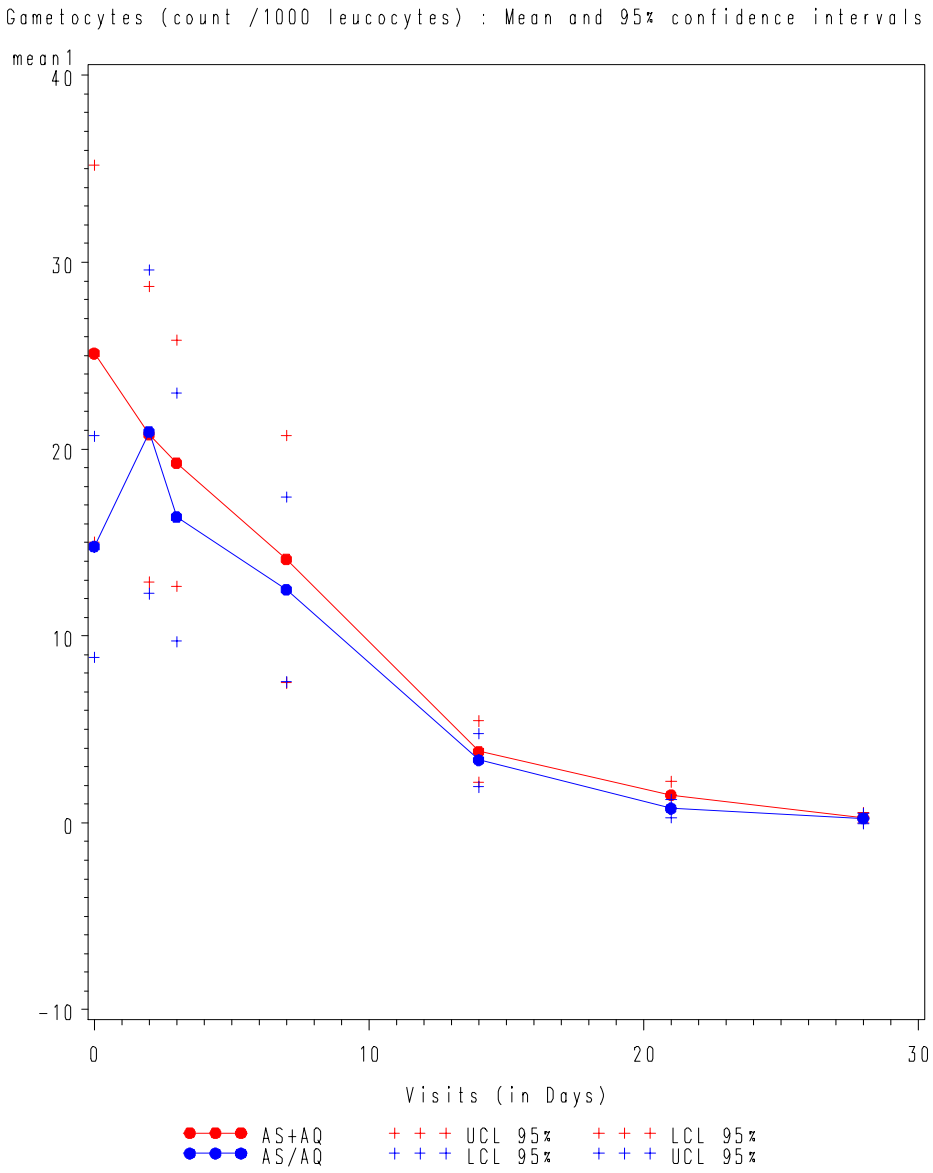
The proportions of gametocyte-carriers present a similar evolution in the 2 groups of treatment. The statistical analysis demonstrated the non-inferiority of AS/AQ compared to AS+AQ for this parameter. Also, a clear decrease in mean gametocyte counts was observed in both groups.
The table below shows the percentage of patients with gametocytes in the PP dataset. The same data are illustrated graphically in the next figure.

Proportions of patients with gametocytes at V1, V3, V4, V5, V6, V7 and V8: PP dataset

Item	Statistic	AS/AQ (N=342)	AS+AQ (N=340)	All (N=682)
Proportion of patients with gametocytes at V1	n / Missing	342 / 0	339 / 1	681 / 1
	n (%)/Yes	48 (14.0)	61 (18.0)	109 (16.0)
Proportion of patients with gametocytes at V3	n / Missing	325 / 17	322 / 18	647 / 35
	n (%)/Yes	93 (28.6)	100 (31.1)	193 (29.8)
Proportion of patients with gametocytes at V4	n / Missing	321 / 21	321 / 19	642 / 40
	n (%)/Yes	84 (26.2)	91 (28.3)	175 (27.3)
Proportion of patients with gametocytes at V5	n / Missing	320 / 22	320 / 20	640 / 42
	n (%)/Yes	74 (23.1)	81 (25.3)	155 (24.2)
Proportion of patients with gametocytes at V6	n / Missing	321 / 21	319 / 21	640 / 42
	n (%)/Yes	42 (13.1)	43 (13.5)	85 (13.3)
Proportion of patients with gametocytes at V7	n / Missing	319 / 23	316 / 24	635 / 47
	n (%)/Yes	14 (4.4)	23 (7.3)	37 (5.8)
Proportion of patients with gametocytes at V8	n / Missing	316 / 26	313 / 27	629 / 53
	n (%)/Yes	4 (1.3)	5 (1.6)	9 (1.4)



The figure below illustrates mean gametocyte counts at each of the study visits.



Time to parasitological cure (time to parasite clearance that is sustained through to D28) and to treatment failure

The actuarial method was used to analyse time to parasitological cure (parasite clearance sustained through to D28) and time to treatment failure. Theoretical visit days were used for the time intervals and the results were consistent with those obtained in the other efficacy analyses for all three analysis datasets

A multinational, randomised, single blind comparative Phase III trial was carried out in Cameroon, Madagascar, Mali, and Senegal, in order to assess the **non inferiority of the new artesunate-amodiaquine fixed dose formulation versus Coartem®**, and to precise the optimal dosing regimen (one or two daily doses).
The primary objective was to demonstrate the non inferiority of Coarsucam™ one daily dose versus Coartem®, according to WHO 2003, Day 28 protocol [20].
The secondary objectives were to compare the three treatment groups in terms of efficacy as per WHO 2003, Day 28 protocol [20], and in terms of clinical and biological tolerability.
The two-sided 90% confidence interval of the difference will be calculated on ITT and PP population (primary analysis will be performed on the ITT one), the acceptance limit for non inferiority was defined as 5 %. Safety will be assessed based on incidence of adverse events, and biological tolerability.
Any subject with malaria attack confirmed by parasitemia was randomly allocated in one of the three regimens, with dosage according to bodyweight range, after informed consent. A 3-day treatment period and 28-day follow-up period was performed. All treatments were administered by an authorised person, without the knowledge of both investigating physician and biologist. In each bodyweight range the total number of tablets was the same, according to the Coartem® reference group, with placebo tablets if necessary.

A total of 941 patients, including **433 children less than 5 years of age, weighing more than 10 kg**, were included in the study between March and December 2006.
The study is completed and data analysis is currently ongoing.

Conclusions on the Efficacy of the fixed dose combination

The analysis of clinical as well as parasitological data of the Burkina Faso study clearly demonstrated the non-inferiority of the fixed artesunate and amodiaquine combination compared to both drugs administered concomitantly. It also confirmed a satisfactory level of efficacy of the combination of artesunate and amodiaquine for the treatment of *Plasmodium falciparum* malaria in children aged 6 months to 5 years (< 18 kg).
The efficacy rate of both treatments in the most clinically meaningful population (mPP dataset) is superior to the 2006 WHO limit of 95% of PCR corrected ACPR level recommended in this target population.
The study had several important secondary outcomes. In keeping with many studies that have used an artemisinin derivative, symptoms and fever resolution was rapid. By Day 2, less than 4% of children were febrile. Similarly, within one week, the majority of children were asymptomatic.
The effect on gametocyte carriage was good in that the proportions of children with gametocytes during follow up was low both for those with gametocytes on Day 0 and for those who developed new gametocytes during follow-up. A reduction in gametocyte carriage results in lower infectivity to mosquitoes, and could lead to a reduction in the transmission of *P. falciparum* malaria in the long term.
It is well known that children under five years of age represent the most difficult population to treat because of their lack of immunity against malaria.

11. Summary of comparative evidence on safety

11.1. Safety and tolerability

- The tolerability to the combination artesunate and amodiaquine has been evaluated through studies involving approximately 4,000 patients. Clinical studies comparing the combined treatment with amodiaquine alone demonstrated no evidence of increased toxicity, even on blood cells, because of the addition of artesunate.
  Most of the reported adverse events may be part of the malarial symptoms present at the initiation of treatment. Common adverse events reported during phase III studies are listed below:

Class-organ	Adverse events
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Headache, dizziness, somnolence
Respiratory, thoracic, and mediastinal disorders	Cold, cough, flu, bronchitis, rhinitis, shivering, sore throat
Gastro-intestinal disorders	Nausea, vomiting, abdominal pain, diarrhea
Skin and subcutaneous tissue disorders	Pruritus
General disorders and administration site conditions	Asthenia, fever
Blood and lymphatic disorders	Reversible asymptomatic neutropenia and leucopenia
Hepato-biliary disorders	Asymptomatic increase of transaminases

- Safety data collected during the Burkina Faso study are developed hereafter.

Common Adverse Events

Over the course of follow up, solicited Treatment-Emergent AEs (TEAEs) were reported by 286 patients out of 375 (76.3%) in the AS/AQ group and 280 out of 374 (74.9%) in the AS+AQ group. The most frequent events were coughing, rhinitis, anorexia, diarrhoea and abdominal pain.

A total of 266 patients (35.5%) experienced at least one TEAE during the study. Incidence was slightly lower in the AS/AQ group: 127 patients out of 375 (33.9%) *versus* 139 out of 374 (37.2%) in the AS+AQ group; the difference was not statistically significant. General disorders and administration site conditions were the most common (mainly fever), reported by 17.3% of patients in the AS/AQ group and 18.4% of patients in the AS+AQ group, followed by gastro-intestinal disorders (mainly diarrhoea or mucous stools), infections/infestations, respiratory disorders and ear disorders.
The proportion of patients experiencing events which were rated by the investigator as possibly or probably related to study drug was very low in both treatment groups [2.4% (9 patients) in the AS/AQ group versus 1.9% (7 patients) in the AS+AQ group].
The main spontaneously reported adverse event possibly or probably related to study drug was somnolence, reported for 6 patients in the AS/AQ group and 5 patients in the AS+AQ group.

TEAEs with Non-Excludable Relationship to Study Treatment: Safety Dataset

	Number (%) of patients		
	Treatment group		
System Organ Class/Preferred Term	AS/AQ N=375	AS+AQ N=374	All N=749
Number of patients with at least one AE	9 (2.4%)	8 (2.1%)	17 (2.3%)
Nervous system disorders	6 (1.6%)	7 (1.9%)	13 (1.7%)
- Convulsion	0 (0.0%)	1 (0.3%)	1 (0.1%)
- Somnolence	6 (1.6%)	5 (1.3%)	11 (1.5%)
General disorders and administration site conditions	2 (0.5%)	1 (0.3%)	3 (0.4%)
- Oedema peripheral	1 (0.3%)	0 (0.0%)	1 (0.1%)
- Pyrexia	1 (0.3%)	1 (0.3%)	2 (0.3%)
Skin and subcutaneous tissue disorders	2 (0.5%)	1 (0.3%)	3 (0.4%)
- Face oedema	1 (0.3%)	0 (0.0%)	1 (0.1%)
- Pruritus	0 (0.0%)	1 (0.3%)	1 (0.1%)
- Skin disorder	1 (0.3%)	0 (0.0%)	1 (0.1%)
Eye disorders	1 (0.3%)	0 (0.0%)	1 (0.1%)
- Ocular icterus	1 (0.3%)	0 (0.0%)	1 (0.1%)

Drug related adverse events resulting in incompletion of study drug

A total of 14 patients, 8 (2.1%) in the AS/AQ group and 6 (1.6%) in the AS+AQ group were withdrawn from the study for repeated vomiting after drug intake on D0 or D1.

Serious Adverse Events and Other Significant Adverse Events

Deaths

Two patients died during the study, both because of the development of severe malaria: (i) patient No. 518 received AS/AQ, and (ii) patient No. 599 received AS+AQ. Both patients were classified as early treatment failures due to severe malaria.

Other serious adverse events

A total of 12 SAEs (6 in each treatment group) occurred during the study, and concerned 9 patients. There was no SAE labelled as possibly or probably related to study treatment. The detail of SAEs is given in the following table. This table shows the number of patients with Serious Adverse Events, as well as the events, by "organ class" and by term. Only one patient in the AS/AQ group was withdrawn from the study due to a SAE (gastroenteritis with dehydration). The relationship of this event to the study drug was considered by the investigator to be improbable.

Serious Adverse Events

	Number (%) of patients					
	AEs			Possibly or probably related AEs		
	Treatment group			Treatment group		
System Organ Class/Preferred Term	AS/AQ N=375	AS+AQ N=374	All N=749	AS/AQ N=375	AS+AQ N=374	All N=749
Number of patients with at least one AE	**4 (1.1%)**	**5 (1.3%)**	**9 (1.2%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
General disorders and administration site conditions	**1 (0.3%)**	**3 (0.8%)**	**4 (0.5%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
- Hyperpyrexia	0 (0.0%)	1 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Hyperthermia	1 (0.3%)	1 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Prostration	0 (0.0%)	1 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations	**1 (0.3%)**	**0 (0.0%)**	**1 (0.1%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
- Gastroenteritis	1 (0.3%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	**1 (0.3%)**	**0 (0.0%)**	**1 (0.1%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
- Dehydration	1 (0.3%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	**3 (0.8%)**	**1 (0.3%)**	**4 (0.5%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
- Convulsion	2 (0.5%)	1 (0.3%)	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Hypertonia	1 (0.3%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	**0 (0.0%)**	**2 (0.5%)**	**2 (0.3%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**

	Number (%) of patients					
	AEs			Possibly or probably related AEs		
	Treatment group			Treatment group		
System Organ Class/Preferred Term	AS/AQ N=375	AS+AQ N=374	All N=749	AS/AQ N=375	AS+AQ N=374	All N=749
- Dyspnoea	0 (0.0%)	1 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Respiratory distress	0 (0.0%)	1 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Laboratory Safety

Biochemistry

One patient ((24 months old, 11 kg) (study number 526, AS+AQ group of treatment) had a D28 AST of 1051 and a D28 ALT of 936 but with a normal total bilirubin. This child was asymptomatic. A.viral hepatitis cannot be excluded because hepatitis serology was not performed.

Uncomplicated *P falciparum* infection causes disease-induced hepatitis that is evidenced by raised liver enzymes and increases in total bilirubin. Malaria-induced haemolysis results in an increase in unconjugated bilirubin. In this study, there was a downward trend in the mean AST and the total bilirubin, consistent with disease resolution but the mean ALT was stable over time, suggesting a small disease effect on this enzyme in these children. The detection of possible drug-induced liver damage is limited in a field trial by the inability to exclude other causes of raised liver enzymes.
Persistence of abnormal 'liver function' tests could be due to continuing recovery of the liver from the effects of malaria. Any other concomitant illnesses e.g. respiratory tract infections or trauma may also result in raised AST and ALT.

The values for other biochemical variables remained stable and no clinically significant changes were observed overall.

Haematology

Descriptive statistics for haemoglobin, haematocrit, white blood cell count (total and differential) and platelet count, measured at D0, D7 and D28 have been calculated by age class and for all age classes, together with the mean changes from visit to visit.

An increase in haematocrit values was observed for all age groups but was small in children aged less than 12 months. An increase in platelet count and eosinophil count was observed from D0 to D7; mean values remained stable from D7 to D28, consistent with recovery from malaria. Most of the values for other haematological variables remained stable.
Neutropenia, defined by investigator as an absolute neutrophil count under 1000/mm^3, concerned 35 patients at D0 (4.9% of the 657 children with neutrophil count data), and 87 patients at D28 (15.3% of the 569 children with neutrophil count data). According to DMID paediatric toxicity table, a large majority of these neutropenias could be graded as mild (750 to 1200/ mm^3) or moderate (400 to 749 / mm^3).

Thus, 29 children (5.1% of the 569 patients with available white cell counts at D28, without difference between the 2 groups of treatment) presented at D28 an absolute neutrophil count < 400/ mm^3.
There was no correlation between neutropenia at D0 and neutropenia at D28. Virtually none of the children with neutropenia presented with fever or clinical symptoms, and no other blood cell lines abnormalities were correlated with these findings.
Amodiaquine is known to induce neutropenia when used as a prophylactic treatment. Few studies of amodiaquine curative treatment have provided information on haematology data at D28. A TDR study performed in Gabon (Adjuik) found that 6% of all enrolled children presented with neutrophil counts < 1000/ mm^3at D28.

Importantly, in the present study, the overwhelming majority of neutropenia findings both at Day 0 (before treatment) and on Day 28 (32/657, 87.5% and 87/569, 97.7% respectively) were made in the first patient recruitment period (October to December 2004), and very few (4/657, 12.5% and 2/569, 2.3% respectively) were made in the second recruitment season (August 2005-January 2006). This strongly suggests the existence of a confounding factor. Two main hypotheses deserve exploring: occurrence of co-morbidities during the first recruitment period that were not seen in the second period (eg viral infection outbreak, although no clinical abnormalities were reported), or changes in laboratory samples management between the two recruitment periods. At the time this report was written, no final explanation had been found for these findings.

Conclusions on Safety

Two patients died during the study due to complications of the initial disease. This study did not otherwise raise particular clinical or biological safety concerns. The incidence of general adverse events was consistent with what can be expected for young patients presenting with malaria. In particular, it is difficult to assign reports of fatigue, nausea, vomiting to the study drugs, the malaria infection itself or to concomitant conditions. Based on what is known of artesunate and amodiaquine safety profile, no unexpected adverse events occurred. There were no reports of allergic side effects that would have contraindicated future drug use such as urticaria, or an erythematous maculopapaular rash. There were no severe cutaneous reactions (erythema multiforme, toxic epidermal necrolysis) even if the number of children in this study was insufficient to detect these rare side effects. Interestingly, no child in the fixed group developed itching and only 2 (0.3%) reported itching in the loose treatment group.
Also, the biochemical and haematological profile is in conformity with the current knowledge on of short-term amodiaquine and artesunate treatment tolerability. Findings of asymptomatic neutropenia, evenly distributed among the two treatment groups, were most probably due to one or more confounding factor.
Finally, the safety profile of artesunate and amodiaquine was shown to be identical in studies with co-administration, therefore one would not expect differences in fixed dose combination tolerability between adults and children.

- **Related to the multinational, randomised, single blind comparative Phase III trial versus** artemether/lumefantrine, the secondary objectives were to compare the three treatment groups in terms of efficacy as per WHO 2003, Day28 protocol [20], and in terms of clinical and biological tolerability.
  Safety is assessed by incidence of adverse events, and biological tolerability. The study is completed and data analysis is currently ongoing.

11.2. Use in pregnancy and lactation

Pregnancy:
Malaria is known to be particularly hazardous during pregnancy. The benefit risk ratio to mother and foetus must be assessed by the prescriber.

- *Artesunate*

Recently published embryofoetal development studies conducted in rats and rabbits suggested a low incidence of cardiovascular malformation and syndrome of skeletal defects at doses close to embryolethal doses and showed evidence of embryotoxicity of the product from the dose of 6 mg/kg/day.
Data on limited number of exposed pregnancies do not indicate any adverse effect of artemisinin on pregnancy or on the health of foetus/newborn child.

- *Amodiaquine*

The safety of amodiaquine in pregnant women has not been conclusively established, although many years of experience with the drug have not indicated a teratogenic potential.

- *Artesunate + amodiaquine fixed dose combination*

In the view of the above mentioned data:
During 1st trimester of pregnancy, artesunate/amodiaquine fixed dose combination tablets should not be used unless clearly necessary e.g. if treatment is life-saving for mother, and if another antimalarial is not suitable or not tolerated.
During 2nd or 3rd trimesters of pregnancy, artesunate/amodiaquine fixed dose combination tablets may be used with caution, only if other antimalarials are unsuitable.
Furthermore, no data is available on the excretion of artesunate/amodiaquine fixed dose combination tablets in breast milk. Breastfeeding continuation can be considered, taking into account artesunate/amodiaquine fixed dose combination tablets safety profile.

11.3. Drug interactions

Artesunate
No pharmacokinetic interactions with other antimalarial drugs of importance have been identified. There is a theoretical risk that a pharmacodynamic interaction with desferrioxamine might attenuate the antimalarial activity of artesunate.

Amodiaquine
Agranulocytosis and hepatitis have been reported following the use of amodiaquine (see Section 15.4.8). Therefore, caution should be observed when prescribing amodiaquine concurrently with other drugs with potential for liver and/or hematological toxicity.

Artesunate + Amodiaquine fixed dose combination

Concomitant administration of Artesunate + Amodiaquine fixed dose combination with other antimalarial treatments is not recommended, as no data on efficacy and safety are available.

Caution should be observed when prescribing Artesunate + Amodiaquine fixed dose combination concurrently with other drugs with potential for liver and/or hematological toxicity (see section 15.4.8).

In the absence of clinical data, Artesunate + Amodiaquine fixed dose combination is not recommended when administered concomitantly with drugs known to inhibit CYP 2A6 (e.g. methoxsalen, pilocarpine, tranylcypromine) and/or 2C8 cytochromes (e.g. trimethoprim, ritonavir, ketoconazole, montelukast, gemfibrozil) (see section 15.5.2).

Though no pharmacokinetic interactions have been documented, amodiaquine and desethylamodiaquine inhibit CYP 2D6 in vitro and may cause clinically significant interactions with some β-blockers, anti-depressants, antipsychotics drugs.

12. Summary of available data on comparative cost and cost - effectiveness within the pharmacological class or therapeutic group

Effective malaria treatments are often not accessible to those who need it, because of their price, inappropriate distribution channels or lack of information. Sanofi aventis has developed a comprehensive program, called Impact Malaria that aims at mobilizing the expertise and resources of a major pharmaceutical manufacturer against malaria.

Develop pricing policies that give access to high quality drugs to all population segments is one segment of the Impact Malaria program. Without compromising quality, production costs have been optimized to offer the lowest possible "no profit-no loss" prices. Drugs are made available through both the public and the private distribution channels to reach all population segments. The same "no profit-no loss" approach is used for sales to the public sector, NGOs, etc.
Our involvement goes beyond the provision of drugs, by supporting projects that will demonstrate what is required for an effective and sustainable control of malaria in a variety of settings.

The pharmaceutical dosage form for paediatric patients is the same than the one for adults. The paediatric formulation is homothetic to the adult formulation and the manufacture is done on the same equipment. This leads to production and cost viability for these paediatric formulations.
Sanofi-Aventis has developed a program that makes drugs available through both the public and private distribution channels to reach all population segments:

- On the private market, the artesunate +amodiaquine fixed dose combination is intended to be available at a target price for children of less than 4 Euros per treatment.

- On the public market, the only fixed dose combination which is comparable to artesunate/amodiaquine is artemether/lumefantrine. Based on the fluctuation of the public tender prices and on the latest tender prices observed, artesunate/amodiaquine fixed dose combination can be estimated to be 50% cheaper than Coartem® at the present time. With a “no profit-no loss” approach, the treatment target price will be approximately 0.8 Euros for adults and 0.5 Euros for children.

In the ERC/International Drug Price Indicator Guide [(21)] there is only one amodiaquine dosage (200mg base) and two artesunate dosages (50 mg and 100 mg) mentioned. As a consequence, it is not possible to establish a real comparison for our three proposed dosages because of lack of data on the artesunate 25 mg tablets dosage price and on the amodiaquine base tablets (67.5 mg, 135 mg, and 270mg) dosages prices.

In parallel, the Mission Pharma Supplier Web site [22] allow to assess the difference in the public treatment cost between Coartem® tablets and the proposed artesunate/amodiaquine fixed dose combination tablets:

Public market -comparative treatment coast

Artemether/lumefantrine **Coartem ®**	Artesunate/amodiaquine **AS+AQ Winthrop®**
Treatment not available	≥ 4.5kg to <9kg : 0.5€
10-14 kg : 0.914$ 15-24 kg: 1.421$ 25-35 kg: 1.929$	≥ 9kg to <36kg : 0.5€
≥ 36kg : 2.437$	≥ 36kg : 0.5€

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

To allow the manufacture of the fixed dose combination, the registration file was first submitted in Morocco on December 7, 2005 and the Marketing/Manufacturing Authorisation was granted on February 1, 2007.
Following this initial registration, several endemic countries have then granted local Marketing Authorisation.
These countries are: Benin, Burkina Faso, Congo, Côte d'Ivoire, Gabon, Guinea, Kenya, Madagascar, Mali, Mauritania, Democratic Republic of Congo, Togo and Zanzibar.
Registration procedures are ongoing in a certain number of other African countries: Burundi, Cameroun, Ghana, Niger, Nigeria, Senegal, Tanzania, Chad and Uganda.

In parallel, on February 23, 2007, Sanofi-Aventis submitted the fixed dose combination dossier to the World Health Organisation, as part of the pre-qualification registration program concerning Artemisinin based antimalarial products.
The dossier is under examination by the WHO assessors.

14. Availability of pharmaceutical standards

Artesunate standards:
- WHO (International Pharmacopoeia, Volume X, 5th edition, 2006),
- In house Standard KNOLL/ABBOTT LIESTAL LTD (Switzerland) according to the International and the European Pharmacopoeias (excepted for the assay, the control of impurities and for the residual solvents tests),
- Chinese and Vietnamese Pharmacopoeia.

Amodiaquine standards:
- WHO (International Pharmacopoeia, Volume X, 5th edition, 2006),
- In house Standard IPCA Laboratories Ltd (India) according to the French Pharmacopoeia (excepted for the assay and for the control of impurities),
- USP 29, NF 24, S2 monograph,
- French Pharmacopoeia.

Fixed dose combination: No standard

15. Proposed (new/adapted) text for the WHO Model Formulary

15.1. NAME OF THE MEDICINAL PRODUCT

Artesunate Amodiaquine fixed dose combination 25mg/67.5mg
Tablet

Artesunate Amodiaquine fixed dose combination 50mg/135mg
Tablet

Artesunate Amodiaquine fixed dose combination 100mg/270mg
Tablet

15.2 CLINICAL PARTICULARS

15.2.1 THERAPEUTIC INDICATION

When prescribing ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION, consideration should be given to official guidance on the appropriate use of antimalarial agents (see also 15.4.4 and 15.5.1).

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is indicated for the treatment of uncomplicated malaria attacks due to *P. falciparum* strains, which are susceptible to the product.

15.2.2 POSOLOGY and METHOD OF ADMINISTRATION

Oral route
Theoretical dosage of artesunate and amodiaquine is adjusted to body weight as follows: 4 mg/kg of artesunate and 10 mg/kg of amodiaquine base once daily for 3 days. However, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION dosage may be adapted according to age or body weight ranges according to the following prescription table, resulting in actual dosing ranges between 2 and 10 mg/kg for artesunate and 7.5 and 15 mg/kg for amodiaquine:

Weight range (approximate age range)	**Product**	**1st day of treatment**	**2nd day of treatment**	**3rd day of treatment**
≥4.5kg to < 9 kg (2 to 11 months)	25mg/67.5mg blister of 3 tablets	1 tablet	1 tablet	1 tablet
≥9kg to <18kg (1 to 5 years)	50mg/135mg blister of 3 tablets	1 tablet	1 tablet	1 tablet
≥18kg to <36kg (6 to 13 years)	100mg/270mg blister of 3 tablets	1 tablet	1 tablet	1 tablet
≥ 36kg (14 years and above)	100mg/270mg blister of 6 tablets	2 tablets	2 tablets	2 tablets

Tablets should be swallowed with a drink of water.
For administration to the youngest children, the tablets can be dissolved in water or crushed and administered with liquid or semi-liquid food.

Should vomiting occur within half an hour after dosing, a repeated dose of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is to be taken. In case of further vomiting, treatment for severe malaria should be considered.

15.2.3. CONTRAINDICATIONS

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION
Hypersensitivity to active substances or to any of the excipients

Amodiaquine
- history of liver injury during treatment with amodiaquine;
- previous hematological event during treatment with amodiaquine.
- retinopathy (in case of frequent treatment).

15.2.4. SPECIAL WARNING AND PRECAUTIONS FOR USE

Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION
ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION has not been evaluated for the treatment of complicated malaria and is therefore not recommended.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION has not been evaluated in the treatment of malaria due to *Plasmodium vivax, Plasmodium malariae* or *Plasmodium ovale* and is therefore not recommended.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION has not been evaluated for malaria prophylaxis and is therefore not recommended.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION has not been studied specifically on patients with thalassemia or sickle cell anaemia.

In absence of specific clinical studies, caution should be exercised in patients with renal insufficiency or liver disease.

Amodiaquine
Toxicity of long term prophylactic treatment with amodiaquine (agranulocytosis, hepatotoxicity) was observed. It is not demonstrated whether this toxicity may develop after repeated cycles of curative treatment.

Symptoms suggestive of the following illnesses should be carefully monitored:
- preicteric phase hepatitis, a fortiori jaundice;
- agranulocytosis (as suggested, for instance by a clinical condition including fever and/or tonsillitis and/or mouth ulcers).

Such symptoms require:
- immediate discontinuation of treatment,
- immediate liver function tests and (or) blood cell counts.

Indeed, in such cases, continuation of treatment with amodiaquine increases the risks of mortality.

Significantly prolonged P, PQ, QRS, and QTc intervals were observed after both 30 and 35 mg of amodiaquine base per kilogram within 3 days but these were not correlated with plasma monodesethylamodiaquine level or associated with clinical events. Caution should be exercised with patients who have recently taken other antimalarial drug with cardiovascular side effects (quinine, quinidine, halofantrine, lumefantrine, mefloquine) or those who are under treatment with cardiovascular drugs. (see section 15.4.9 overdosage).

15.2.5. INTERACTION WITH OTHER MEDICINAL PRODUCT AND OTHER FORMS OF INTERACTION

Artesunate
No pharmacokinetic interactions with other antimalarial drugs of importance have been identified. There is a theoretical risk that a pharmacodynamic interaction with desferrioxamine might attenuate the antimalarial activity of artesunate.

Amodiaquine
Agranulocytosis and hepatitis have been reported following the use of amodiaquine (see Section 15.4.8). Therefore, caution should be observed when prescribing amodiaquine concurrently with other drugs with potential for liver and/or hematological toxicity.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION
Concomitant administration of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION with other antimalarial treatments is not recommended, as no data on efficacy and safety are available.

Caution should be observed when prescribing ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION concurrently with other drugs with potential for liver and/or hematological toxicity (see section 15.4.8).

In the absence of clinical data, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is not recommended when administered concomitantly with drugs known to inhibit CYP 2A6 (e.g. methoxsalen, pilocarpine, tranylcypromine) and/or 2C8 cytochromes (e.g. trimethoprim, ritonavir, ketoconazole, montelukast, gemfibrozil) (see section 15.5.2).

Though no pharmacokinetic interactions have been documented, amodiaquine and desethylamodiaquine inhibit CYP 2D6 in vitro and may cause clinically significant interactions with some β-blockers, anti-depressants, antipsychotics drugs.

15.2.6. PREGNANCY AND LACTATION

Pregnancy:
Malaria is known to be particularly hazardous during pregnancy. The benefit risk ratio to mother and foetus must be assessed by the prescriber.

- *Artesunate*

Recently published embryofoetal development studies conducted in rats and rabbits suggested a low incidence of cardiovascular malformation and syndrome of skeletal defects at doses close to embryolethal doses and showed evidence of embryotoxicity of the product from the dose of 6 mg/kg/day. (See section 15.5.3).
Data on limited number of exposed pregnancies do not indicate any adverse effect of artemisinins on pregnancy or on the health of foetus/newborn child.

- *Amodiaquine*

The safety of amodiaquine in pregnant women has not been conclusively established, although many years of experience with the drug have not indicated a teratogenic potential.

- *ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION*

In the view of the above mentioned data:
During 1st trimester of pregnancy, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION should not be used unless clearly necessary e.g. if treatment is life-saving for mother, and if another antimalarial is not suitable or not tolerated.
During 2nd or 3rd trimesters of pregnancy, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION may be used with caution, only if other antimalarials are unsuitable.

Lactation:
No data is available on the excretion of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION in breast milk. Breastfeeding continuation can be considered, taking into account ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION's safety profile.

15.2.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients receiving ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION should be warned that somnolence, dizziness or asthenia may occur in which case they should not drive or use machines.

15.4.8. UNDESIRABLE EFFECTS

The adverse events are ranked under body-system and frequency using the following convention: very common: ≥1/10; common: ≥ 1/100 to <1/10; uncommon: ≥ 1/1000 to < 1/100; rare: ≥1/10,000 to < 1/1000; very rare : < 1/10,000; not known: cannot be estimated from the available data.

Artesunate
The tolerability to artemisinins has been evaluated through studies involving 8844 patients and from post-marketing studies and experience.

Class-organ	Adverse events
Blood and lymphatic disorders	Common : neutropenia (but not agranulocytosis) Uncommon : reduced reticulocytes count, anemia
Nervous system disorders	Very common: headache, dizziness Rare : convulsions
Cardiac disorders	Common: mild electrocardiogram (ECG) changes (QTc and PR increases), atrial extrasystoles, non specific T- wave changes
Gastro-intestinal disorders	Very common: nausea, vomiting, abdominal pain, diarrhea
Hepato-biliary disorders	Uncommon: transaminases increase

Amodiaquine

The following adverse reactions have been reported with amodiaquine, especially at higher doses and/or during prolonged treatment:

- Blood and lymphatic system disorders: cases of leukopenia and neutropenia (agranulocytosis),
- Nervous system disorders: rarely, neuromyopathy,
- eye disorders, varying in type and severity: transient accommodation disorders, corneal opacifications regressive once treatment is stopped, very rarely, irreversible retinopathy justifying specialist ophthalmic attention,
- Hepato-biliary disorders: severe cases of sometimes fatal hepatitis,
- Skin and subcutaneous disorders: slate-gray pigmentation, notably affecting the fingers and mucous membrane.

Artesunate and amodiaquine free combination

The tolerability to the combination artesunate and amodiaquine has been evaluated through studies involving around 4,000 patients. Clinical studies comparing the combined treatment with amodiaquine alone demonstrated no evidence of increased toxicity, even on blood cells, because of the addition of artesunate.
Most of the reported adverse events may be part of the malarial symptoms present at the initiation of treatment. Common adverse events reported during phase III studies are listed below:

Class-organ	Adverse events
Metabolism and nutrition disorders	anorexia
Nervous system disorders	headache, dizziness, somnolence
Respiratory, thoracic, and mediastinal disorders	Cold, cough, flu, bronchitis, rhinitis, shivering, sore throat
Gastro-intestinal disorders	nausea, vomiting, abdominal pain, diarrhea
Skin and subcutaneous tissue disorders	pruritus
General disorders and administration site conditions	Asthenia, fever
Blood and lymphatic disorders	Reversible asymptomatic neutropenia and leucopenia
Hepato-biliary disorders	Asymptomatic increase of transaminases

Artesunate amodiaquine fixed combination

The tolerability to the fixed combination artesunate amodiaquine has been evaluated through one study conducted in Burkina-Faso and involving around 750 children (under 5 years of age). This study comparing the fixed dose combination with the free combined treatment did not show any unexpected adverse event.

For special warning and precautions for use, see Section 15.2.4.

If any of the side effects is serious or unexpected, you should inform the Marketing authorisation holder and/or health authority, as per local regulation.

15.2.9. OVERDOSE

In cases of suspected overdose, the patient should be urgently transferred in a specialized unit where appropriate monitoring and symptomatic and supportive therapy should be given.

Artesunate
No overdose cases have been reported so far.

Amodiaquine

- Dangerous dose of amodiaquine cannot be stated precisely because of the low number of known cases; by analogy with chloroquine, it can be estimated at around 2 grams as a single administration in adults.
- Symptoms: headache, dizziness, visual disorders, cardiovascular collapse and convulsions, followed by brutal and early respiratory and cardiac arrest.

15.3. PHARMACOLOGICAL PROPERTIES

15.3.1. PHARMACODYNAMIC PROPERTIES

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION
ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is an artemisinin base combination therapy which consists, as recommended by the World Health Organization (WHO), of the simultaneous administration of at least two blood schizonticides, with independent modes of action and different intraparasitic biochemical targets.
Namely, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is indicated in areas where parasite resistance rate to amodiaquine remains below the recommended levels.

Up to date, efficacy and safety of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION in uncomplicated malaria were evaluated in Africa.

ARTESUNATE: *Antimalarial (ATC code: P01BE03).*
Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide extracted from a plant used in traditional Chinese medicine, known as sweet or annual wormwood (Artemisia annua).

The chemical mechanism of action of artesunate has been widely studied and appears well established. The artesunate endoperoxide bridge is split by heme within the infected erythrocyte, generating singlet oxygen. Parasite proteins, particularly in membranous structures, are thus alkylated, leading to parasite death.

In-vitro 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 inactive ring stage to late schizontes. The schizonticidal and gametocytocidal activities of artesunate, administered orally have been demonstrated in vivo on chloroquine-sensitive strains of Plasmodium (*P. berghei* in mice and *P. knowlesi* in monkeys) and on chloroquine-resistant strains (*P. berghei* in mice).

In-vitro Artesunate appears to be inactive against extra-erythrocyte forms, sporozoites, liver schizontes or merozoites.

When administered orally, artesunate consistently acts more quickly than orally- administered chloroquine and intravenous quinine in all animal models studied, regardless of the strain or dose tested. In macaques (the animal model most similar to humans) infected with a chloroquine-resistant strain of *P. knowlesi*, cure was obtained with the same dose of artesunate and quinine.

General pharmacology studies have shown that artesunate, administered at a dose equal to at least 50 times the therapeutic dose used in humans, did not affect the central nervous, cardiovascular or respiratory systems in the animal models tested.

AMODIAQUINE: *Antimalarial (ATC code: P01BA06).*
Amodiaquine is a synthetic 4-aminoquinoline antimalarial. Its activity is characterized by a schizonticidal action on *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. Therefore, it is used to treat acute illnesses by destroying intraerythrocytic forms.

The mechanism of action of 4-aminoquinoline derivatives against plasmodium is not yet completely known. It is nonetheless accepted that these derivatives, one of which is amodiaquine, penetrate the infected red blood cells in a specific way and prevent the parasite from polymerizing heme into an insoluble product called hemozoin, leading to parasite death.

Strains of *Plasmodium falciparum* resistant to 4-aminoquinolines (chloroquine, amodiaquine) are present in many areas, and their geographical distribution is constantly changing. However, amodiaquine remains active against many chloroquine-resistant *P. falciparum* strains.

15.3.2. PHARMACOKINETIC PROPERTIES

Artesunate

- **Absorption**

The pharmacokinetic parameters of a single dose of artemisinin derivatives are not affected by food.

After oral administration, absorption is rapid followed by major transformation into dihydroartemisinin (DHA).

Following oral artesunate, a significant increase in C_{max} and area under the curve (AUC) of DHA was observed in patients with malaria compared with healthy subjects, although neither the time to attain these concentrations nor the ultimate elimination of the metabolite was affected.

- **Distribution**

The target organ for artesunate is the red blood cell, with preferential accumulation in infected erythrocytes with Plasmodium falciparum. *In vitro* studies have shown that DHA accumulation was 300 times greater than in non infected red blood cells.
In man, artesunate is poorly protein bound.

- **Metabolism**

Artesunate is extensively metabolized. Its main metabolite, DHA is the most active artemisinin derivative.

After oral or intravenous administration, artesunate is transformed into DHA by blood esterases and by certain liver cytochromes, particularly CYP2A6. DHA is then eliminated after glucuronoconjugation.

No significant interaction between artesunate and some other antimalarials (pyronaridine, chloroquine, amodiaquine) were evidenced by in-vitro and in-vivo (proguanil-atovaquone) studies. In in-vitro tests in the presence of human liver microsomes, artesunate does not significantly inhibit carboxy-mefloquine formation but of carboxy-primaquine formation.

- **Elimination**

Excretion of artesunate in humans has not been fully investigated. Preclinical data suggests that artesunate is essentially metabolised as less than 1% of the dose is recovered as parent drug (urines, feces and bile).

Amodiaquine

- **Absorption**

After oral administration in healthy subjects, amodiaquine is quickly absorbed and transformed in its main active metabolite, the desethylamodiaquine.

- **Distribution**

In-vitro studies have shown that the oxidative metabolism of amodiaquine leads to the formation of the two intermediates, semi-quinoneimine and quinoneimine, which irreversibly bind to proteins, particularly to human and mouse liver microsomal enzymes.

Monodesethylamodiaquine, the main metabolite of amodiaquine, is mainly found in blood, at much higher concentrations than unchanged amodiaquine. Its concentration in whole blood is 4-6 times higher than in plasma. It is assumed to be the sole derivative that contributes significantly to the antimalarial activity in the blood.

- **Metabolism**

Amodiaquine is metabolized via desethylation, oxidation and glucuronoconjugation. Hepatic first-pass metabolism in the liver is high, and the monodesethylamodiaquine is the primary source of antiparasite activity. The main metabolic pathway of amodiaquine leading to monodesethylamodiaquine is via the cytochrome CYP 2C8 isoenzym.

- **Elimination**

Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine.
Seven-day urinary excretion of monodesethylamodiaquine and an unknown metabolite total around 8.5% of the administered dose.

Artesunate and amodiaquine interaction

After single dose administration, pharmacokinetic properties of each compound and its active metabolite were not markedly affected whether the drugs were administered alone or in combination.

Artesunate and amodiaquine combination

Pharmacokinetic parameters of amodiaquine (AQ), desethylamodiaquine (desethylAQ), artesunate (AS) and dihydroartemisinin (DHA), after administration of two ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION tablets (i.e total dose of 540 mg amodiaquine and 200 mg artesunate) in healthy volunteers (n=32) are summarized in the following table:

	AQ	Desethyl AQ	AS	DHA
Tmax (h)	1.33 ± 1.61	2.90 ± 1.63	0.42 ± 0.25	0.72 ±0.25
Cmax (ng/ml)	9.18 ± 2.99	147.89 ± 61.3	162.93 ± 122.06	460.4 ± 175.58
AUCo-t (ng.h/ml)	65.74 ± 29.90	9947.8 ± 4312.3	89.88 ± 45.40	712.2 ± 253.35
AUCo-∞ (ng.h/ml)	89.84 ± 39.66	11451 ± 6836.7	97.82 ± 49.68	718.95 ± 257.13
T½ (h)	9.93 ± 4.18	689.18 ± 356.55	0.50 ± 0.38	1.66 ± 0.58

Special population
Patients with liver disease: The pharmacokinetics of artemisinin derivatives are unchanged in subjects with liver cirrhosis.
No specific study has been conducted in special populations with ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION.

15.3.3. PRECLINICAL SAFETY DATA

No specific preclinical studies in co-administration were performed. Preclinical data were generated for both compounds.

Preclinical data have been generated from both compounds alone.

The main preclinical results are summarized below:

- General toxicity :
***Artesunate*:** artesunate's toxicity appears in rat and dog after repeated oral administration of doses ≥ 50 and 82.5mg/kg/day, respectively, i.e. 12.5 and 20.6 times the proposed therapeutic dose in man. In both species, toxicity is expressed as bone marrow changes (hypoplasia in both myeloid and erythroid populations with some regeneration at lower doses as expressed by increases in reticulocyes which then decrease at the severely toxic doses), liver and renal lesions (rat only) in addition to lymphoïd hypoplasia in the dog only (decrease in circulating lymphocytes).
***Amodiaquine*:** no data on the toxicity of amodiaquine after repeated oral administration to animals are available.

- Genotoxicity:
***Artesunate*:** *in vitro* tests (Ames test) and *in vivo* tests (micronucleus in mice) did not show any mutagenic potential.
Amodiaquine: *in vitro* (Ames test) and *in vivo* tests (sister chromatid exchange and chromosome aberration tests) showed that amodiaquine, like chloroquine, is slightly mutagenic.

- **Carcinogenesis:** No studies of the carcinogenic potential of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION or the products examined separately have been conducted.

- **Study of reproductive function :**
Artesunate: Embryofetal development studies recently published in rats and rabbits according to ICH protocols showed a low incidence of cardiovascular malformation and syndrome of skeletal defects at doses close to embryolethal doses. The no or low adverse effect levels were in the range of 5 to 7 mg/kg/day. In these same studies the compound showed evidence of embryotoxicity from the dose of 6 mg/kg/day.

Amodiaquine: No data on amodiaquine toxicity on the reproductive system and embryofetal development is available. Some data on the teratogenic effects of chloroquine, another 4-aminoquinoline derivative is summarized below: chloroquine is teratogenic at high doses, between 250 and 1500 mg/kg, in animals, with a fetal mortality of 25%. At 1000 mg/kg, eye malformations can be seen in 45% of animals. Moreover, autoradiographic studies have shown that chloroquine administered at the start or the end of the gestation period accumulates in the eyes and ears. In rats, lower doses retard growth and higher doses cause malformations of the skeleton. The injection of a 40mg/kg dose of chloroquine at the end of the gestation period in rat leads to delayed lung maturation in the foetus.
Results obtained with chloroquine suggest that the compound has some embryofetotoxicity when administered during gestation. As amodiaquine has a similar chemical structure, it too might be teratogenic.

- Safety pharmacology studies
***Artesunate*:** artesunate depresses all the major body functions (gastro-intestinal, respiratory and cardiovascular systems) at very high doses in rat and cat, i.e. generally after intravenous administration of doses exceeding 300 mg/kg , which is the equivalent of about 75 times the recommended clinical dose administered orally. Renal function appears to be affected at relatively lower doses (from 12 mg/kg followed by infusion of 0.024 mg/min for one hour in the rat).
***Amodiaquine*:** No « standard » safety pharmacology assessments have been conducted on amodiaquine. Only a certain number of specific studies have been conducted retrospectively to explain the adverse effects observed in man particularly after administration for the prevention of malaria.

15.4. PHARMACEUTICAL PARTICULARS

15.4.1. SHELF LIFE
The shelf life of the product as packaged for sale is 24 months.

15.4.2. SPECIAL PRECAUTIONS FOR STORAGE
The product should be stored below 30°C in the original package.

15.4.3. NATURE AND CONTENTS OF CONTAINER
ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION 25mg/67.5mg
3 tablets packaged in an aluminium/aluminum blister pack

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION 50mg/135mg
3 tablets packaged in an aluminium/aluminum blister pack

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION 100mg/270mg
3 tablets packaged in an aluminium/aluminum blister pack, for children between 6 and 13 years of age.
6 tablets packaged in an aluminium/aluminum blister pack, for patients aged 14 years and older.

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