

**IND Protocol: Intravenous Artesunate for
Treatment of Severe Malaria in the United States**

IND Sponsor: Centers for Disease Control and Prevention (CDC)

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1.0 SUMMARY:

Currently, there are no Food and Drug Administration (FDA) approved therapeutics for treatment of severe malaria in the United States (US). Previously, intravenous (IV) quinidine gluconate was the only parenteral drug available in the US that was FDA-approved for the treatment of severe malaria. However, in November 2017, the manufacturer of IV quinidine (Eli Lilly Pharmaceuticals) ceased production of quinidine permanently and remaining stocks of quinidine expired on March 31, 2019. A well proven alternate treatment, recommended by the World Health Organization (WHO) in preference to quinidine and used worldwide for the treatment for severe malaria, is artesunate. Artesunate, however, has not yet been approved by the Food and Drug Administration (FDA) for use in the US. Through an expanded access Investigational New Drug (IND) program, CDC has made IV artesunate available for treatment of severe malaria under an IND protocol with IV artesunate product produced by the Walter Reed Army Institute of Research (WRAIR). We propose to make this intravenous GMP IV artesunate available to malaria patients hospitalized in the US who need IV treatment because of severe disease, high parasitemia, or inability to take oral medications. The drug will be provided to the hospitals, upon request for a patient with severe malaria. The IV artesunate will be followed by oral treatment with artemether-lumefantrine (Coartem™), atovaquone-proguanil (Malarone), doxycycline, clindamycin, or mefloquine to ensure maximal curative effect. The receiving physicians will be requested to notify CDC of any adverse event following administration of the drug.

2.0 BACKGROUND

2.1 Severe malaria

Severe malaria is a major global health problem. An estimated 440,000 deaths are caused annually by severe malaria, with the majority of deaths occurring in young children (WHO 2017). Severe malaria is a medical emergency whose treatment has become increasingly difficult due to the advent and spread of drug-resistant parasites. This situation has been improved by the introduction of artemisinin derivatives, whose life saving properties reside in their rapid action and their efficacy against multidrug-resistant parasites.

Severe malaria results from the infection of a large number of red blood cells by malaria parasites. Of the four species of malaria parasites that infect humans (*Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*), almost all cases of severe malaria are due to *P. falciparum*. There have been rare case reports of severe manifestations of disease associated with *P. vivax* infection (Hwang 2014).

The large-scale destruction of parasitized red blood cells releases biologic products harmful to the infected host. The sequestration of infected red blood cells in the small vessels of vital organs such as the brain or kidneys leads to end-organ dysfunction. The resulting manifestations of severe malaria include those listed in Table 1.

Table 1: Clinical and laboratory features of severe malaria (WHO 2015)

Cerebral malaria
Generalized convulsions
Severe anemia
Hypoglycemia
Metabolic acidosis
Acute renal failure
Acute pulmonary edema, acute respiratory distress syndrome (ARDS)
Circulatory shock
Abnormal bleeding
Disseminated intravascular coagulation
Jaundice
Hemoglobinuria
High fever
Hyperparasitaemia

Despite appropriate therapy and medical care, mortality from severe malaria remains high. Case fatality rates were 7.3% - 17.7% in children admitted with severe malaria to a Kenya hospital (Marsh 1995), and 3-15% in European patients admitted in European hospitals (Mühlberger 2003, Krause 2006). The case fatality rate in the United States is estimated to be 1% (Newman 2004).

2.2 Severe malaria in the United States

In the United States, malaria is now a rare disease; for this reason, it is not always recognized, diagnosed and treated in time and correctly. In 2016, there were more than 2000 diagnosed cases of malaria in the US reported to the CDC (CDC 2019). Almost all of these cases occur in persons who, after acquiring the infection in a malaria endemic area abroad, are diagnosed after return to the US (“imported malaria”). Most of these patients are US residents who have no acquired immunity to malaria and are, therefore, at risk of developing severe disease. A major contributing factor to continued malaria-associated mortality in the United States is delay in initiation of appropriate treatment (Newman 2004). In the five-year period between 1999-2004, there were 41 deaths from severe malaria in the United States (RD Newman, unpublished).

Based on surveillance data, an estimated 300 cases of complicated malaria requiring parenteral treatment occur every year in the US.

2.3 Diagnosis and treatment of severe malaria in the United States

A provisional diagnosis of severe malaria can be made in a patient who presents any of the features cited in Table 1, and who has malaria parasites demonstrated on microscopic examination of a blood smear. In most cases, the parasite will be identified as *P. falciparum*. In some cases the parasites will be identified as *P. vivax*, *P. ovale*, or *P. malariae*, or a combination of the four species; or the microscopic examination may detect malaria parasites without being able to identify them specifically as being *P. falciparum* (diagnosis: *Plasmodium*, species undetermined). Because microscopic diagnosis is not always accurate (especially in the US, where laboratory personnel are not always familiar with malaria), a patient with the features of severe malaria (Table 1) and malaria parasites of any species should be treated as if having *P.*

falciparum, the species responsible for practically all cases of severe malaria. Treatment for *P. falciparum* will be effective against the blood stage of all four malaria species.

In some patients suspected of having severe malaria based on travel history, clinical findings, and exclusion of other causes of illness, a reliable microscopic diagnosis cannot be secured in a timely manner due to lack of laboratory facilities or trained personnel. Such patients can justifiably be treated presumptively for severe malaria, because the risk of death due to untreated severe malaria outweighs the risk of fatal adverse events caused by a presumptive (and possibly unnecessary) treatment.

Patients with severe malaria in the US should be treated with IV administration of a rapidly acting antimalarial drug (previously quinidine, now IV artesunate) (www.cdc.gov/malaria; hereafter will be referred as CDC malaria website 2019). Parenteral treatment aims to rapidly reach parasitocidal blood levels of the antimalarial drug, thus lowering the level of parasitemia and reversing end organ dysfunction and hemolysis. Although parenteral treatment is life-saving, because of its rapid action it often fails to eliminate all parasites; therefore, adjunct therapy is needed. Treatment with a follow-on, different drug ensures curative treatment through complete elimination of all remaining malaria parasites and includes artemether-lumefantrine, atovaquone-proguanil, doxycycline, clindamycin, or if these drugs are not available, mefloquine (CDC malaria website 2019).

In addition, general supportive care should be given which may include infusion of intravenous fluids; correction of metabolic disturbance such as hypoglycemia or acidosis; blood transfusions; assisted ventilation; vasopressors; and renal dialysis (WHO 2015; CDC malaria website 2019).

Response to therapy should be assessed by clinical observations and measurements of laboratory parameters such as serial blood smears. The goals for treatment should be decrease in parasitemia and eventual parasitemia clearance.

In addition to patients with severe malaria, patients who are unable to ingest drugs orally due to nausea and vomiting (a frequent complication of malaria) should also receive parenteral therapy.

3.0 QUINIDINE

Quinine, a quinolinemethanol that is a component of the bark of cinchona trees, is the oldest known antimalarial drug and remains a key component in the treatment of severe malaria. Parenteral quinine is not commercially available in the United States, where by default severe malaria has historically been treated since 1991 with the D-isomer of quinine: quinidine (CDC 1991). The sole drug manufacturer of quinidine ceased production in 2017 and quinidine is no longer available for use in the US as of March 31, 2019.

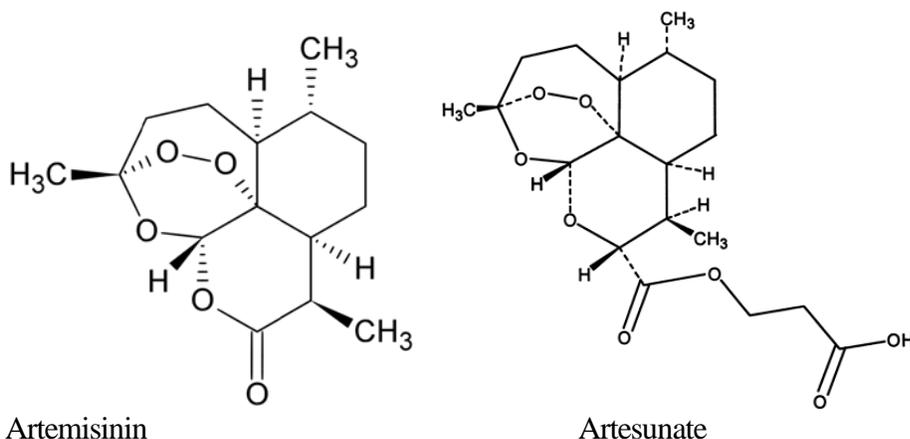
4.0 ARTESUNATE

Artesunate is an artemisinin derivative with excellent safety and efficacy data for the treatment of severe malaria. The WHO Guidelines for Treatment of Malaria (2015) recommend artemisinin derivatives as an essential component in the treatment of malaria (including severe malaria) worldwide (WHO 2015). While artemisinin derivatives have wide global availability and clinical usage, they have not yet been approved by the FDA for use in the United States.

WRAIR-manufactured IV artesunate is available for use under this CDC-sponsored IND 76,725/CDC IRB Protocol # 5032 for the treatment of severe malaria in the US; however, due to limited remaining stock of the WRAIR-manufactured product and anticipated increase in demand for IV artesunate due to quinidine unavailability, CDC will also provide IV artesunate manufactured by Guilin Pharmaceutical under CDC-sponsored IND 76,725/CDC IRB Protocol # 7171 for the treatment of severe malaria.

4.1 Artemisinin and its derivatives

Artemisinin is extracted from the “qinghaosu” or sweet wormwood plant (*Artemisia annua* L.) which has been part of traditional Chinese herbal medicine for centuries. Artemisinin was rediscovered and isolated in 1972 by Chinese scientists seeking new treatments for drug-resistant malaria, and was first reported in the medical literature in 1979. It is a sesquiterpene lactone with an internal peroxide linkage (Klayman 1985). The mechanism of antimalarial action of artemisinin has been hypothesized to involve an iron-mediated cleavage of the endoperoxide bridge, which produces oxygen radicals, which then react with nearby molecules, interfering with parasite function (Meshnick 1994). Various derivatives of artemisinin differ by the substituent at position #10. They include dihydroartemisinin, artemether, arteether, and artesunate. Artesunate is the hemisuccinate of the ester of dihydroartemisinin. It is water based, and rapidly biotransforms to its active metabolite, dihydroartemisinin, which has a short half-life of approximately 1 hour. Artemisinin derivatives have been used for more than two decades and are now a key component of treatment of malaria worldwide. They are available in formulations that allow administration by different routes (oral, parenteral, rectal). WHO supports their use as first-line antimalarial drugs, in combination with other antimalarial agents, in most malaria- endemic areas of the world. Such artemisinin-based combination therapies (ACT) aim to treat drug-resistant *P. falciparum* malaria rapidly and successfully, while at the same time slowing the emergence of resistance to artemisinin (WHO 2006).



4.2 Artesunate: Efficacy

Experimental studies have demonstrated the efficacy of artesunate against malaria parasites cultured *in vitro*, and against malaria parasites in experimental animal models (rodent and non-human primates).

Artesunate has been used extensively to treat malaria for more than two decades outside the US.

Given intravenously, it has been highly effective, and has the advantage of a reliable and rapid pharmacokinetic profile. Studies on the treatment of severe malaria have been conducted in China, India, Thailand, Burma, Vietnam, Brazil, Ghana, Sudan, Gabon, and Malawi. These studies have utilized artesunate intravenously, intramuscularly, and rectally, alone and in combination with other drugs. Trials up to 1999 were summarized in the Cochrane Review Series (McIntosh and Olliaro, 2000). For the purposes of this protocol, only trials that employed intravenous artesunate for treatment of severe malaria are summarized below.

A study of 79 Vietnamese adults compared IV artesunate plus mefloquine, artemisinin suppositories plus mefloquine, and IV quinine. It demonstrated that IV artesunate cleared parasitemia and fever significantly faster than IV quinine, but no significant differences were found in duration of coma or mortality (Hien, 1992). Earlier unpublished studies (TK Anh, 1989) comparing artesunate to IV quinine in 41 Vietnamese adults, and follow-up unpublished studies by the same author (TK Anh) in 190 Vietnamese adults from 1992 to 1995 showed statistically significant differences in mortality favoring artesunate. A study in Myanmar among 141 Burmese adults with cerebral malaria showed significantly less mortality in the artemisinin-derivative arms (which included an arm with IV artesunate plus mefloquine) when compared with the IV quinine plus tetracycline arm (Win 1992).

A randomized, open-label trial compared IV artesunate and IV quinine in 113 adults with severe malaria in two centers in Thailand (Newton 2003). Mortality was 12% in the artesunate arm and 22% in the quinine arm (relative risk 0.53; $p=0.22$), suggesting that artesunate is at least as effective as quinine. Importantly, parasite clearance times were shorter and fewer patients developed hypoglycemia on artesunate therapy.

The largest and most definitive trials on the efficacy of artesunate were two multicenter, open-label randomized control trials implemented by the South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group and the African Quinine Artesunate Malaria Trial (AQUAMAT) group. The SEAQUAMAT trial enrolled 1,461 patients with severe malaria in Bangladesh, India, Indonesia and Myanmar (SEAQUAMAT 2005). The trial was stopped early as researchers witnessed a significant reduction in mortality in the artesunate arm (15%) compared to the quinine arm (22%) with a relative risk of 0.69 (95% CI 0.54-0.83). The number of patients needed to receive treatment with artesunate to save one life, in comparison to patients treated with quinine, ranged from 11.1 to 20.2, depending on the countries. Artesunate was well tolerated while quinine was significantly associated with hypoglycemia. The AQUAMAT trial enrolled 5425 children in 11 African countries (AQUAMAT 2010). Mortality among those given artesunate (8.5%) was significantly lower than those given quinine (10.9%) with an odds ratio (adjusted for study site) of 0.75 (95% CI 0.63-0.90) and a relative reduction in mortality of 22.5% (95% CI 8.1-36.9; $p=0.0022$). There were no serious adverse events associated with artesunate, while quinine was associated with post-treatment hypoglycemia. The authors in both studies recommended that artesunate become the treatment of choice for severe *P. falciparum* malaria.

The evidence-based 2015 WHO Guidelines for Treatment of Malaria consider artemisinin derivatives to be an essential component in the treatment of severe malaria (WHO 2015).

4.3 Artesunate: Toxicity

Clinical and animal studies suggest that artemisinin derivatives are much less toxic than the quinolones, the group that includes quinine and quinidine (Price 2000). The safety profile of artesunate is well established from decades of use and in the published literature. Furthermore, dose ranging and pharmacokinetic studies have demonstrated that artesunate does not accumulate. The studies are summarized below.

4.3.1 Preclinical studies

Animal preclinical data suggest that the most common side effects of artemisinin derivatives might be reversible reticulocytopenia and mild hemolysis, of unknown mechanism (RS Miller, WRAIR, 2004 unpublished data). Neutropenia and diarrhea were seen in primates, but not in dogs. At high doses in non-human primates (>32 mg/kg), transient ataxia and hypersalivation have been observed. Toxicity studies of IV artesunate given for 14 days to beagle dogs detected no adverse effects except for a decrease in red blood cell parameters, including reticulocytes.

Toxicity studies of beagle dogs given escalating doses of IV artesunate detected no cardiovascular or respiratory adverse effects. Toxicity studies in experimental animals (including rodents, monkeys, and dogs) demonstrated neurotoxic effects affecting mostly the brain stem (Miller and Blanchard, 2003). Such neurotoxicity has not been found in humans, which suggests that their occurrence in experimental animals were due to the high doses administered or the formulation used (Gordi and Lepist 2004).

The most important concern about this drug class has been the neurotoxicity reported in animals with the long-acting intramuscular oil-based artemisinins, such as artemether and arteether (Brewer 1998, Gordi and Lepist 2004). All the artemisinins, including artesunate are metabolized to dihydroartemisinin. Most experiments on artemisinins contain too many confounding variables to definitively determine the cause and mechanism of neurotoxicity, particularly since severe malaria may itself cause decreased neurologic function. Li et al (2002) concluded from studies with rats that prolonged drug exposure at low levels was related to a greater likelihood of severe neurotoxicity of artemisinin derivatives.

4.3.2 Human data

Artemisinin derivatives appear to be safe and have been used to treat several millions of cases of malaria without reported serious adverse events. Price (1999) combined findings from studies conducted in western Thailand during which 3,276 patients were treated orally with artesunate, of whom 2,646 also received mefloquine; 386 were treated with artemether, of whom 180 also received mefloquine; and 1,303 were treated with mefloquine alone. Symptomatic side effects in the pooled group of patients treated with artesunate or artemether monotherapy ranged from 34% (anorexia on Day 1-2), to 15-16% (dizziness-nausea on Day 1-2), to 1% (diarrhea on Day 1-2), and were generally less than the incidence of side effects in the mefloquine monotherapy group (54%, 54%-46%, and 3%, respectively). There was no evidence of neurotoxicity, cardiotoxicity, or allergic reactions attributable to the artemisinin derivatives. Adverse events (AEs) were noted in 17 patients, all of whom had received mefloquine either as monotherapy (2), in combination with artesunate (13) or with artemether (2). No AEs were noted in patients who had received artesunate monotherapy. The AEs consisted of urticaria, hemoglobinuria, seizures, neuropsychiatric reactions, and reversible neurologic changes, and could have resulted from malaria, mefloquine, or the artemisinin-based drugs.

Severe allergic reactions have been reported in case reports. Two out of 17,000 patients treated with artemisinin derivatives in Thailand developed pruritus and urticarial rashes, and dyspnea following oral artesunate (Leonardi 2001). Among 59 patients with severe malaria treated with IV artesunate in western Thailand, one patient developed an urticarial rash (Newton 2003).

Pharmacokinetic studies of intravenous artesunate at a range of doses have demonstrated the short half-life of both artesunate, and its active metabolite, dihydroartemisinin. (Li 2009 and Miller 2012). A single dose of 0.5, 1, 2, 4, or 8 mg/kg of artesunate found half-lives ranging between 0.12-0.24 and 1.15-2.37 hours for artesunate and dihydroartemisinin, respectively (Li 2009). Another study gave subjects multiple escalating intravenous doses of 2, 4, and 8 mg/kg of artesunate over three days, and found no accumulation of the drug (Miller 2012).

4.3.3 Particulates in artesunate produced for clinical use

Small amounts of dihydroartemisinin may be present as particulates in the 10 to 25 micron range in the currently available clinical lot of artesunate produced for clinical use. The U.S. Pharmacopeia (USP) has established acceptable levels of particulates present at the ≥ 10 -micron range. USP <788> sets these limits of acceptability for particle counts for vials less than 25 mL at less than 6000 particles/vial for the ≥ 10 micron range. Although all tests for particulates to date have been within the acceptable range, on January 18, 2008, CDC received particulate results that were in the upper range of the acceptable limits. All currently available laboratory evidence to date suggests that these particles are dihydroartemisinin, the active metabolite of artesunate which is less soluble in water than artesunate. When this product is administered through a 0.8-micron hydrophilic polyethersulfone filter, particulate counts are reduced to an essentially particulate free solution. While the Artesunate Integrated Product team at Walter Reed believes the presence of these particles do not necessarily pose a risk to patients receiving the product, use of the filter negates the possibility of effect without influencing the efficacy of the product. Thus, CDC is now recommending that artesunate should be administered using a 0.8 micron hydrophilic polyethersulfone syringe filter.

4.3.4 Delayed hemolytic anemia after treatment for severe malaria with artesunate

Between 2010 and 2012, 19 instances of delayed hemolytic anemia have been reported in the published literature following treatment of severe malaria with artesunate in other non-endemic countries (Kano 2010; Zoller, Junghanss et al. 2011; Caramello, Balbiano et al. 2012; Kreeftmeijer-Vegter, van Genderen et al. 2012; Rolling, Schmiedel et al. 2012). As of September 2012, CDC recommended that persons treated for severe malaria with artesunate be evaluated weekly for up to 4 weeks after that treatment for evidence of hemolytic anemia. Weekly laboratory evaluation should include hemoglobin, reticulocyte count, haptoglobin, lactate dehydrogenase (LDH), and total bilirubin. Post-artesunate delayed hemolysis is a nonrecurring event characterized by a 10% or greater decrease in hemoglobin levels in the setting of a haptoglobin level <0.1 g/L and an increase of LDH levels to >390 U/L, or an increase of $\geq 10\%$ over baseline at least 7 days after initiation of parenteral artesunate treatment. Five cases of delayed hemolytic anemia have been identified in the United States after the use of WRAIR-supplied artesunate for the treatment of severe malaria under this IND protocol. Artesunate kills the intraerythrocytic malaria parasites which are then removed from the red blood cells

by the spleen. The leading hypothesis for the occurrence of delayed hemolytic anemia is that the previously infected red blood cells have a decreased life span compared to red blood cells that were never infected. So rather than being lysed by the parasites at the time of the severe malaria episode, the red blood cells are cleared by the spleen about 7-14 days after the treatment with artesunate in a self-limited hemolytic event. Persons with higher parasitemias seem to have a higher likelihood of delayed hemolytic anemia after treatment with artesunate. Depending on the amount of hemolysis, transfusion may be needed. Any instances of hemolytic anemia after treatment with artesunate should be reported within 24 hours to the principal investigators, Dr. Francisca Abanyie-Bimbo (404) 718-4775 or Dr. Kathrine Tan at (404) 718-4701.

4.4. Artesunate and pregnancy

The information below is referenced from IND 64, 769, “The summary of studies on the adverse effects of AS on pregnancy of humans and animals: studies reported in literature and conducted in house” which summarizes the literature and current studies at WRAIR:

- Artesunate causes fetal toxicity in rats and rabbits resulting in fetal resorption and abortion, as well as a low incidence of cardiac malformations and skeletal defects.
- Studies in rats at WRAIR indicate that artesunate crosses the placental barrier and accumulates in the placenta and fetus, which may explain the observed fetal toxicity.
- From 1999 to 2006, a total of 2,045 pregnant women participating in clinical trials in Thailand, the Gambia, and Sudan were treated with artesunate alone or in combination with other antimalarial drugs (such as quinine, mefloquine, atovaquone-proguanil and sulfadoxine-pyrimethamine). Most of these patients were in the second and third trimesters of pregnancy. The investigations found no significant differences from community rates in birth weight, duration of gestation, placenta weights, or congenital abnormality rates in newborns at delivery or in growth and developmental parameters of infants monitored for one year.

McGready (2001) assessed artesunate safety in western Thailand, where 461 pregnant women were treated with artemisin derivatives (predominantly artesunate) with no evidence of adverse effects. In 414 women with known pregnancy outcomes, the rates of abortion (4.8%), stillbirth (1.8%), congenital abnormalities (0.8%), and low birth weight (19.0%) did not differ significantly from rates found in the community. The vast majority of study participants were in their second or third trimesters of pregnancy. In 44 women who received artemisinin derivatives during the first trimester of pregnancy, the abortion rate was not significantly different from the community rate.

Moore (2016) conducted an observational study of 55,636 pregnancies on the Thai-Burma border between 1994 and 2013, assessing the effects of instances of malaria during the first trimester as well as the effects of different malaria medicines on rates of miscarriage and major congenital malformations. There was no difference in those rates for women treated with artemisinins compared to those treated with quinine. The conclusion from this article is that artemisinins including artesunate appear to be safe for use during the 1st trimester of pregnancy

Thus, while animal studies indicate that artesunate can have harmful effects on pregnancy, no such effects have been documented in humans. Ongoing studies continue to demonstrate the safety of artemisinins during pregnancy. Considering that severe malaria represents a substantial risk for pregnant women and their fetuses, WHO recommends that pregnant women with severe malaria be treated with artesunate or quinine in the first trimester, and with artesunate preferentially to quinine in the second and third trimesters (WHO 2006).

5.0 ARTESUNATE: PRODUCT SOURCE AND DESCRIPTION

5.1 Product

The investigational product to be used in this protocol is the WRAIR's formulation of IV artesunate, WR256283. The product will be provided as a sterile dry-filled powder with a diluent for reconstitution, phosphate buffer. Once reconstituted, the drug should be administered through a 0.8 micron polyethersulfone syringe filter as a precautionary safety measure regarding any potential precipitation of the product.

The bulk drug was purchased from Knoll Pharmaceuticals, and manufactured by SRI International, Menlo Park, CA, US, Batch # 14462-16 (Bottle # BR 29487). It was produced in September – October 2004. Scheduled stability and degradation studies will be conducted at regular interval to ensure the drug's chemical stability. Only drug products with a current certificate of analysis will be used. . No expired drug will be used. The drug label will also contain the following: Store at 2 – 10 degrees Celsius. CAUTION: INVESTIGATIONAL NEW DRUG LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE.

The phosphate buffer (USP), also manufactured by SRI International, Menlo Park, CA, US, Lot #: 090403-B, will be used as diluent for artesunate in this trial. The phosphate buffer will be stored at 2° to 30° Celsius.

IV Artesunate (WR256283) will be supplied with a certificate of analysis and a statement of the expiration or re-test date. CDC will provide the investigational product that has been packaged to prevent contamination or deterioration during transport and storage.

5.2 WRAIR trials with product

The product was used by WRAIR in several clinical trials under IND 64,769. A single-dose pharmacokinetic and safety study demonstrated the virtual lack of any measurable side effects in doses approaching currently up to 8 mg/kg, nearly four times the recommended dose. Minor, extremely transient side effects consisted of minor lightheadedness in up to 40% of the participants at the time of infusion and an alteration of taste (metallic taste) in up to 50% of the participants (prior to breaking the code). (Li 2009)

In a pharmacokinetic study of this cGMP IV artesunate, multiple doses of this cGMP IV artesunate up to 8 mg/kg were given to healthy volunteers. No accumulation of artesunate or its active metabolite, dihydroartemisinin were observed. (Miller 2014)

In a phase 2 trial in Kenya, adults with non-complicated *P. falciparum* malaria were treated with this cGMP IV artesunate at the same drug regimen as proposed in this CDC program. No major adverse events were noted in 30 subjects. The pharmacokinetics and efficacy of the product were comparable to those of previously used (non-ICH cGMP) artesunate preparations. (Li 2014)

A review of 128 patients with severe malaria treated with this cGMP IV artesunate from January 2007 through December 2010 found mortality to be 6.9%, and the most frequent adverse events (anemia and elevated hepatic enzymes) were attributed to the severity of the malaria. (Twomey 2015)

6.0 OBJECTIVE

The primary purpose of this program is to make available intravenous artesunate for treatment of severe malaria in US hospitals because parenteral quinidine is no longer available. CDC should be notified of adverse events associated with the administration of artesunate for reporting in accordance with 21 CFR 312.32.

7.0 TREATMENT DESIGN

7.1 Inclusion Criteria/Eligibility

In order to be eligible for IV artesunate, a patient must meet the following criteria:

- a. Malaria confirmed by microscopy. It is expected that the great majority of the eligible cases will be diagnosed as *P. falciparum*. Patients with other microscopic diagnoses of malaria (*Plasmodium* of undetermined species, or species other than *falciparum*) will also be eligible, taking into account the unfamiliarity of some US laboratories with malaria diagnosis and the importance of timely treatment of severe malaria. In exceptional cases, microscopic diagnosis might be waived, e.g., a patient with strong clinical suspicion of severe malaria, for whom a timely, reliable microscopic diagnosis is not available (current CDC guidelines advise that in such cases, parenteral antimalarial treatment is justified).
- b. Parenteral treatment required due to one or more of the following reasons (1, 2, or 3):
 1. Unable to take oral medications
 2. High density parasitemia ($\geq 5\%$)
 3. Severe malaria based on:
 - i. Impaired consciousness
 - ii. Seizures
 - iii. Circulatory collapse/shock
 - iv. Pulmonary edema or acute respiratory distress syndrome (ARDS)
 - v. Acidosis
 - vi. Acute kidney injury
 - vii. Abnormal bleeding or disseminated intravascular coagulation (DIC)
 - viii. Jaundice (must be accompanied by at least one other sign of severe malaria)
 - ix. Severe anemia (Hb < 7 g/dL)

7.2 Exclusion Criteria

- a. Known allergy to artesunate

7.3 Special considerations: Pregnant Women

For pregnant women, especially in the first trimester of pregnancy: the lack of data regarding potential artesunate teratogenicity must be weighed against the risks of severe malaria in the context of quinidine unavailability or unsuitability. Ultimately, malaria is life threatening for both the pregnant woman and the fetus, and artesunate should not be withheld if quinidine is unavailable, contraindicated, ineffective, and/or not tolerated.

7.4 Procedures

- a. Malaria Branch medical epidemiologists who take CDC Malaria Hotline clinical calls from physicians will determine eligibility using the “Eligibility for IV Artesunate” form (Appendix I).
- b. If the patient meets eligibility criteria and the attending physicians agree, CDC Malaria Branch staff will fax and/or email the required consent form (Appendix V) and drug administration protocol (Appendices II, III) to the physician or other health care provider.
- c. CDC Malaria Branch staff will initiate the procedure for release of IV artesunate from the CDC Drug Service or Quarantine Station to the appropriate treatment facility (Appendix IV).
- d. Artesunate will be released from CDC Drug Service or Quarantine Station to the treatment facility as rapidly as possible (ground courier or air).
- e. Artesunate will be administered at the health facility, with a treating physician serving as a site investigator. Consultation with CDC medical epidemiologists as needed.
- f. **All Serious Adverse Events (SAE) associated with IV AS treatment must be reported to CDC within 24 hours by telephone.** The Adverse Event Report form (Appendix III) should be completed and sent to CDC within 10 calendar days by fax, email, or regular mail. *See Appendix III for appropriate contact information.*

8.0 ADMINISTRATION OF ARTESUNATE AND FOLLOW-ON TREATMENT

8.1 Artesunate

The investigational product IV artesunate (WR256283) will be provided as a sterile dry-filled powder and will be prepared for administration by reconstitution in the sodium phosphate buffer prior to infusion.

Reconstitution and administration of IV artesunate:

The formulation of artesunate consists of two parts. Part A is a vial filled with base artesunate, the active component; Part B (diluent) is a vial filled with phosphate solution used to dissolve the artesunate in Part A just prior to administration. Specifically, 11 ml of diluent will be withdrawn from the diluent vial (Part B) and injected into the artesunate vial (110 mg of artesunate) (Part A). This mixture will be gently swirled for 5 to 6 minutes (resulting in a concentration of 10 mg/ml) and will be administered within 1 hour. The reconstituted drug will be injected intravenously (through

an established intravenous line or needle) pushed over 1-2 minutes through a 0.8-micron polyethersulfone syringe filter that is provided in the artesunate packet.

Schedule and dosage of IV artesunate:

Per WHO guidelines, consistent with the pivotal SEAQUAMAT and AQUAMAT trials, 3-doses of IV artesunate, administered intravenously slowly over 1-2 minutes, at 12-hour intervals (0, 12, and 24 hours) is recommended for treatment of severe malaria. If after completion of the third dose, the patient can tolerate oral medications and has $\leq 1\%$ parasitemia oral medications can be given. If after the third dose the patient is unable to tolerate oral medications, or parasitemia is $>1\%$, artesunate can be administered daily for up to 6 additional days (not to exceed a total of 7 day treatment equaling 9 doses in total) or until the patient can tolerate oral medications and parasitemia is $\leq 1\%$. If the patient cannot tolerate oral medications and/or has continued high parasitemia ($>1\%$), requiring additional IV artesunate doses, contact the CDC Malaria Hotline at 770-488-7788 from 9:00am to 5:00 pm Eastern time or after hours call the CDC Emergency Operations Center at 770-488-7100. Ask to speak with the malaria clinician on call for a consultation and request regarding additional IV artesunate doses.

The following weight-based dosing should be used to calculate the correct dose for administration:

- **Adults and children ≥ 20 kg:** 2.4 mg/kg at 0 hour, 12 hours, and 24 hours
- **Children < 20 kg:** 3.0 mg/kg at 0 hour, 12 hours, and 24 hours

The dose in persons > 20 kg is the same dosage as used in the SEAQUAMAT trial. The slightly higher dosage in children < 20 kg is in line with the WHO-recommended dosage based on pharmacokinetic modeling demonstrating a larger volume of distribution in children of that size. (WHO 2015)

8.2 Follow-on treatment

Please note that the follow-on treatment is not part of this program and will not be provided by CDC.

WHO recommends that after 24 hours of IV artesunate, oral medication can be used if the patient is able to tolerate medications by mouth. This is consistent with the sentinel IV artesunate efficacy trials, SEQUAMAT and AQUAMAT. Because of its rapid action, artesunate is used initially to reduce the parasitemia as quickly as possible. Then, once the patient is able to tolerate oral medication and has a parasitemia $<1\%$, a treatment course of oral antimalarials can be used to ensure curative treatment through complete elimination of all remaining malaria parasites. Because IV artesunate has a short half-life (less than 2 hours), potential drug-drug interactions should not be an issue. Treating physicians should make sure to use an appropriate follow-on drug to complete the treatment of malaria. The choice of which follow-on drug to use is at the discretion of the treating physician. The follow-on oral drug should be initiated at least 4 hours after the last IV dose of artesunate. Treating physicians should choose to use one of the drug regimen recommended by CDC against chloroquine-resistant *P. falciparum* (CDC malaria website, 2019), by order of preference:

8.2.1 Artemether-lumefantrine (Coartem™), is the follow-on drug of first choice, and will be given to most patients.

A 3-day treatment course is recommended for both adult and pediatric patients based on weight (see below). The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 oral dose twice daily for the following 2 days (a total of 6 doses over 3 days).

1 tablet = 20mg artemether/ 120 mg lumefantrine

5 - <15 kg: 1 tablet per dose
15 - <25 kg: 2 tablets per dose
25 - <35 kg: 3 tablets per dose
≥35 kg: 4 tablets per dose

Artemether-lumefantrine can be used in second and third trimesters of pregnancy. It can be used in the first trimester of pregnancy if no other drug options are available. It is not recommended in infants weighing <5 kg.

8.2.2 Atovaquone-proguanil (AP, Malarone)

Atovaquone-proguanil was also the oral follow-on drug used in previous clinical studies of IV artesunate in Kenya. AP has been studied in combination with oral artesunate for treatment of uncomplicated malaria and no evidence of cardiotoxicity was found (Gupta 2005).

Atovaquone-proguanil is available in two strengths, adult (250 mg atovaquone/100 mg proguanil) and pediatric (62.5 mg atovaquone/25 mg proguanil).

Adults will receive AP 1 g/400 mg (four adult tabs) every day for 3 consecutive days.

Children will receive AP doses based upon body weight as indicated below.

5 – 8 kg: 2 peds tabs po every day for 3 consecutive days
9 – 10 kg: 3 peds tabs po every day for 3 consecutive days
11 – 20 kg: 1 adult tab po every day for 3 consecutive days
21 – 30 kg: 2 adult tabs po every day for 3 consecutive days
31 – 40 kg: 3 adult tabs po every day for 3 consecutive days
> 40 kg: 4 adult tabs po every day for 3 consecutive days

Note: AP is not recommended for infants under 5kg.

8.2.3. Quinine and doxycycline (or clindamycin for children under 8 years and pregnant women) will be the follow-on drugs for patients who cannot take AL or AP, or if AL or AP are not available. Adult dosage of quinine: 542 mg base (650 mg salt) po tid for 3 days (7 days if malaria from Southeast Asia), and doxycycline: 100 mg po bid for 7 days. Pediatric dosage (children 8 years or older) of quinine 8.3 mg base/kg (10mg salt/kg) po tid for 3 days (7 days if malaria from Southeast Asia), and doxycycline 4 mg/kg/day divided bid for 7 days. Children under 8 years of age

or pregnant women should receive quinine as dosed above, and clindamycin 20 mg base/kg/day divided tid for 7 days.

8.2.4 Mefloquine, although a highly efficacious antimalarial, will be the follow-on drug of last choice because of the relatively high rate of adverse drug reactions in persons who receive treatment doses of mefloquine. Adult dosage: initial dose of 750 mg salt po followed by 500 mg salt 6-12 hours after initial dose; pediatric dosage: 15 mg salt/kg po as initial dose, followed by 10 mg salt/kg po given 6-12 hours after initial dose.

8.3 Patients still not tolerating oral medications after 3 doses of IV artesunate within 24-hour period:

If parasitemia is <1% but the patient after three doses administered at 12-hour intervals (0, 12, and 24 hours) of IV artesunate but the patient still cannot tolerate oral medications several treatment options are available, depending on the patient's clinical and parasitological status. The most suitable course of treatment should be selected by the attending clinicians in consultation with CDC. Potential options include:

1. Continue IV artesunate, dosed once a day, up to additional 6 days. The total course should not exceed 7 days (a total of 9 doses).
2. Switch to treatment with IV doxycycline (7 days) or IV clindamycin (7 days).

(These regimens are described more in detail on the CDC website https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html).

As soon as the patient can tolerate oral medications, switch to an appropriate oral follow-on treatment.

8.4 Unused IV artesunate

IV artesunate is provided under an Investigational New Drug protocol, therefore any unopened and unused product should be returned to:

CDC DRUG SERVICE, D-09
1600 CLIFTON RD.
ATLANTA, GA 30333
Telephone: 404-639-3670

These unused vials should be shipped at 2 -10°C (35 -50°F) using an expedited shipper who guarantees delivery within 24 hours. Additional details can be found in Appendix VI.

9.0 SUPPORTIVE CARE AND FOLLOW-UP

Patients should be treated in intensive care units, and should receive appropriate supportive treatment required by their clinical status (e.g., fluid administration, transfusions, assisted ventilation, vasopressors, etc.).

A thin blood smear should be prepared and read by an experienced microscopist to determine baseline parasite density, expressed as a percent of red blood cells infected. Blood smears should be repeated every 12 - 24 hours until at least two consecutive blood smears are negative, and also at the end of treatment.

Any adverse events (AE) potentially associated with the administration of artesunate should be treated appropriately.

10.0 SAFETY DATA COLLECTION AND REPORTING

Attending or treating physicians are responsible for the real-time collection and evaluation of safety data. The occurrence and outcome of all AEs meeting the AE definition below should be documented to the extent possible, including relevant clinical data and concomitant medication for patients who experience an AE during and up to 28 days post completion of IV artesunate treatment course. All AEs meeting reporting criteria (see definitions below) should be documented on the Adverse Event Reporting Form (Appendix III), and faxed, emailed, or mailed to the Principal Investigators within 10 days of AE occurrence. All SAEs should be notified to the Malaria Branch by telephone within 24 hours of occurrence and followed up with a completed Adverse Events Report Form (Appendix III) which should be faxed, emailed, or mailed to the Principal Investigators within 10 days of SAE occurrence. Please be informed that cases of delayed hemolysis occurring up to 28 days after IV artesunate treatment should be reported as an AE. Appendix III including the Supplemental Form for Delayed Hemolysis should be completed and submitted to CDC.

The Principal Investigator and Sub-investigators at the CDC Malaria Branch may request additional information from attending physicians for their review of SAEs.

Definitions of Adverse Events (AEs)

An ADVERSE EVENT (AE) is any untoward medical occurrence associated with the use of a drug/biologic in humans, whether or not considered related to artesunate. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of artesunate, without any judgment about causality, that was not present prior to initiation of IV artesunate treatment. Any medical condition or laboratory abnormality that was present prior to IV artesunate treatment should be considered as a baseline condition and not an AE. However, if an existing medical condition deteriorates at any time during and through 28 days post completion of IV artesunate treatment, it should be recorded as an AE. Complete Appendix III for all AEs.

A SUSPECTED ADVERSE REACTION is any AE for which there is a reasonable possibility that artesunate caused the adverse event. It is a subset of all AEs for which there is a reasonable possibility that artesunate caused the event. “Reasonable possibility” means there is evidence to suggest a causal relationship between artesunate and the AE. “Suspected adverse reaction” implies a lesser degree of certainty about causality than “adverse reaction.”

An ADVERSE REACTION is any AE caused by artesunate. Adverse reactions are a subset of all suspected adverse reactions for which there is a reason to conclude that artesunate caused the event.

UNEXPECTED: An AE is considered “unexpected” if it is not listed in this protocol or is not listed at the specificity or severity observed.

SERIOUS: An AE or suspected adverse reaction is considered “serious” if in the view of either the treating physician or CDC, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

LIFE-THREATENING: An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the treating physician or CDC, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused a death.

CDC Reporting Requirements to FDA and CDC IRB

Upon receipt of reported AEs from treating physicians, CDC will review to determine any suspected adverse reactions that are both serious and unexpected. Any adverse events that are determined to be serious and unexpected will be reported to FDA within 15 calendar days. Per 21 CFR 312.32, a suspected adverse reaction is determined based on evidence to suggest a causal relationship between artesunate and the AE, such as:

- a) A single occurrence of an event that is uncommon and known to be strongly associated with artesunate.
- b) One or more occurrences of an event that is not commonly associated with artesunate, but is otherwise uncommon in patients who received artesunate for treatment.
- c) Aggregate analysis of specific events observed in this treatment program that indicates those events occur more frequently in the patients treated with artesunate than in a concurrent or historical control group in which no artesunate treatment was given.

CDC will also report to FDA within 15 calendar days any clinically important increase in the rate of a serious suspected adverse reaction and any findings from clinical studies or animal studies or in vitro testing that suggest a significant risk in humans exposed to artesunate. Unexpected fatal or life-threatening suspected adverse reactions will be reported to FDA as soon as possible and no later than 7 calendar days after CDC’s initial receipt of the information. CDC will also report AEs and incidents to CDC IRB according to CDC IRB’s policy and procedures.

AE Follow-Up

All AEs should be followed to resolution to the extent possible and outcomes classified as recovered, sequelae, death, or lost-to-follow-up. Additional information may be requested by CDC to complete AE follow-up.

11.0 DATA COLLECTION, HANDLING, AND RECORDKEEPING

In requesting and obtaining IV artesunate under this IND, treating physicians are responsible for data collection, handling, and recordkeeping pertaining to patients receiving IV artesunate under their care in accordance with the IND protocol. Treating physicians should complete the Demographics forms and the Treatment Plan forms (Appendix I and II) and submit them to CDC. Adverse Event forms (Appendix III) should be completed and returned to CDC if the patient experiences an AE. To the extent practicable, safety information should be collected on cases experiencing AEs, during and up to 28 days after IV artesunate treatment and reported to CDC according to the timeframes indicated above in Section 10.0 (initial phone notification on SAEs within 24 hours of occurrence, followed by completed Appendix III form within 10 days of occurrence; For AEs, Appendix III form within 10 days of occurrence).

As IV artesunate is an investigational drug, the requesting or treating physician and his/her delegated entities (e.g., hospital pharmacy) are responsible for product accountability regarding record keeping of IV artesunate receipt, use/administration, and return as outlined in Appendix VI (Investigational Drug Accountability and Return Form). Completed form must be returned to CDC Drug Service by fax (404-639-3717) or email scanned copy to drugservice@cdc.gov. If unused, unopened vials are returned to CDC, also include a copy of the completed investigational drug accountability form (Appendix VI) in the shipment.

CDC Drug Service will document all releases through its secure database. CDC Malaria Branch will manage data collection and submitted patient data including reports of AE will be kept in a secure database. All data from AE cases will be included in the evaluation of safety.

12.0 Program Modifications

Changes or modification to the existing protocol should not be implemented without a formal amendment to the protocol except to eliminate an immediate risk to patients. If protocol amendments necessitate a change in the informed consent form (ICF) it may be necessary for a participant currently receiving treatment under the protocol to be informed about the revision and asked to sign the revised ICF. A copy of the revised, signed (with date) ICF should be given to the participant and all original versions of the ICF retained as part of the participant's permanent record. Copies of signed ICF will be retained at CDC.

13.0 PROGRAM RESPONSIBILITIES

13.1 Principal Investigators

The Principal Investigator is responsible for coordinating the activities and implementation of the protocol with the Malaria Branch staff and the CDC Drug Service as well as monitoring the safety of participants receiving IV artesunate.

13.2 CDC Malaria Branch Medical Officers/Epidemiologists

CDC Malaria Branch Medical Officers/Epidemiologists will respond to clinical calls and will

evaluate all severe malaria cases to determine eligibility and, if necessary, initiate the protocol. The Malaria Branch Medical Officers/Epidemiologists will be responsible for initiating drug delivery and conducting follow-up phone calls.

13.3 Clinicians in Healthcare Facilities

Clinicians are responsible for determining whether the patient fulfills criteria for administration of artesunate; contacting CDC; administering the drugs as described in the protocol; and

reporting to CDC any AEs recorded during the program—whether or not considered to be related to the administration of artesunate.

14.0 ETHICAL, Legal, and Administrative Requirements

14.1 Current Good Clinical Practice (cGCP)

The procedures set forth in this program are designed to ensure that the Sponsor and all program personnel abide by the Code of Federal Regulations (in particular, 21 CFR, Parts 56, 312, 314, and 600) and ICH Guidelines for GCP. By signing Form FDA 1572 (Investigator’s Agreement Form), each treating physician is agreeing to abide by these regulations and guidelines.

14.2 Informed Consent

Written informed consent, either from each participant or the participant’s legal guardian, in compliance with 21 CFR 50, must be obtained before any program-related procedures are initiated. The ICF must be dated, witnessed, and retained by the investigator as part of the program records at the medical facility administering the product. Each participant will receive a copy of the signed ICF and any revised ICF. If the signed form is lost, the participant will be required to sign and date a new ICF before receiving subsequent treatment. Because artesunate will be used for a potentially life-threatening illness, the ultimate responsibility for decision making for this product for all minors should be the parent or guardian.

Informed consent includes the principle that it is critical that the individual be informed about the potential risks and benefits of participating in this program. This information will allow individuals to make a personal risk-versus-benefit decision and understand the following general principles:

1. Participation in this program is entirely voluntary.
2. Participants may withdraw from participation in this program at any time without penalty or loss of benefits to which they are otherwise entitled.
3. Refusal to participate in this program involves no penalty.
4. The individual is free to ask any questions that will allow him/her to understand the nature of this program.

If a patient is unable to respond and make wishes known about artesunate treatment, and no next-of-kin or legal representative is available, and the patient’s illness is life-threatening, per 21 CFR 50.23 “Exception from General Requirements”, informed consent may be deemed not feasible and the treating physician can make the determination to administer artesunate. Per 21 CFR 50.23, the patient’s treating physician, acting as site investigator, and a physician who is not otherwise participating in this expanded access IND treatment program, will document the following on the consent form and will return a copy of the consent form to CDC.

1. Patient is confronted by a life-threatening situation necessitating the use of artesunate.
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.
3. Time is not sufficient to obtain consent from the patient’s legal representative.

4. There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

CDC will also report the above to CDC IRB as required and according to CDC IRB's policy and procedures.

If immediate use of artesunate is, in the treating physician's opinion, required to preserve the life of the patient, and time is not sufficient to obtain the independent determination required above in advance of administering artesunate to the patient, the determinations of the treating physician shall be made and, within 2 working days after the use artesunate, be reviewed and evaluated in writing by a physician who is not participating in this treatment protocol.

14.3 Risks

The risks to the patients include:

1. Accidental disclosure of private identifiable information
2. Risks inherent to the procedures needed for the diagnosis and treatment of severe malaria
3. Risks of AEs and SAEs, or lack of treatment effectiveness.

To minimize the risks of disclosure of private information, the patients' records and identifiable databases will be kept under conditions of confidentiality routinely followed in hospitals. At CDC, the participants' records will be kept in locked, secure storage areas at the Drug Service and at the Malaria Branch. To minimize the risks inherent to diagnostic and treatment procedures and the risks of AE and SAEs, all medical personnel and CDC investigators will exercise due care in the management of the patients. These risks are justifiable in relation to the anticipated benefits to the patient, namely treatment of a potentially fatal disease with an effective, rapidly-acting antimalarial drug.

14.4 Inclusion of children

Any person with severe malaria in the US requires appropriate IV antimalarial treatment, and IV artesunate is the only option in the US. Therefore, those treated with IV artesunate under this IND may include those in vulnerable populations. This protocol is greater than minimal risk, but presents the prospect of direct benefit to patients. The risk of adverse drug reaction is far outweighed by the benefit of being treated for severe malaria, a potentially fatal disease. The relation of the anticipated benefit to the risk is more favorable than that of other available treatments, as one of the eligibility criteria for this treatment is that other available treatments are not clinically appropriate.

In accordance with 21 CFR 50.55, permission will be sought from a parent or guardian. Minors who are legally able to give consent under local laws will not be considered children.

14.5 Privacy and Confidentiality

Participant identification number and date of birth will identify participants in a secure CDC database. Participants should be advised that they could be contacted by telephone or by mail at later dates for follow-up through their treating physician. This follow-up includes safety surveillance.

Representatives of the Sponsor, drug manufacturer, and the FDA are eligible to photocopy and review medical and program records related to this program as a part of their responsibility to protect human participants in this program.

No personal data will be used in any external communication or publication.

15.0 FINANCING AND INSURANCE

The CDC is funding this program. Should a participant be injured as a direct result of participating in this program, he/she will receive medical care for that injury. Should a participant require medical treatment, the costs for hospital and medical care will not be covered by the CDC and will need to be paid by the participant, the participant's insurer, Medicare, or Medicaid. The participant should be informed that this does not constitute a waiver or release of legal rights. The investigators or designees should discuss this issue with the participant or legally authorized representative at the clinical site.

16.0 PUBLICATION P O L I C Y

All data collected during the course of this program may be published in the open medical literature with the identity of the participants protected.

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APPENDICES

APPENDIX I:	DEMOGRAPHICS
APPENDIX II:	TREATMENT PLAN
APPENDIX III:	ADVERSE EVENT REPORT FORM
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APPENDIX I

Participant ID:

Study Inclusion

Determining eligibility:

A patient is eligible to receive intravenous (IV) artesunate treatment if at least one criterion is satisfied in EACH of sections A and B.

Section A: (Malaria diagnosis). One of the following criteria must be satisfied:

- Malaria confirmed by microscopy
- Strong clinical suspicion of severe malaria, but timely microscopic confirmation is not possible, and parenteral treatment with antimalarial drug is urgently needed.

Section B: (Need for IV treatment). At least one of the following criteria must be satisfied (Check all that apply):

- Unable to take oral medication
- Parasitemia $\geq 5\%$ (parasitemia: _____)
- Impaired consciousness
- Seizures
- Circulatory collapse/shock (vasopressors used: YES NO)
- Pulmonary edema or acute respiratory distress syndrome
- Acidosis
- Acute kidney injury (BUN: _____ creatinine: _____)
- Abnormal bleeding or disseminated intravascular coagulation (DIC)
- Jaundice (bilirubin: _____) [must be accompanied by one other severe criteria]
- Severe anemia with hemoglobin under 7 gm/dL (hemoglobin: _____)

DOES THE PATIENT MEET ELIGIBILITY CRITERIA? YES NO

(At least one criterion in each of the sections A and B)

*: *Precautions concerning artesunate:*

-Patients with known allergy to artesunate or other artemisinin derivatives should not receive artesunate

- For pregnant women, especially women in the first trimester of pregnancy: the lack of data regarding potential artesunate teratogenicity must be weighed against the risks of severe malaria in the context of quinine unavailability or unsuitability. Ultimately, malaria is life-threatening for both the pregnant woman and the fetus, and artesunate should not be withheld if quinidine is unavailable or unsuitable.

Date informed consent form signed (mm/dd/yyyy): ____ / ____ / ____

Participant ID:

Demographics

1. Today's date(mm/dd/yyyy): _____
2. CDC Epidemiologist: _____
3. Station delivering artesunate: _____
4. Patient's Name: _____
5. Patient's Medical Record Number: _____
6. Patient's Date of Birth(mm/dd/yyyy): _____
7. Patient's Gender: Male Female
8. Is Patient of Hispanic or Latino ethnicity? Yes No
9. Check the *primary* race of the patient. If patient considers him/herself of more than one race, check 'Other' and specify the races:

<input type="checkbox"/> White	<input type="checkbox"/> Asian
<input type="checkbox"/> Black or African American	<input type="checkbox"/> Native Hawaiian or Other Pacific Islander
<input type="checkbox"/> American Indian or Alaska Native	<input type="checkbox"/> Other, specify races: _____

10. Is the patient pregnant: Yes No N/A

If yes, how many weeks? _____

11. Parasite species: Pf Pv Po Pm (Check all species that apply)
 Unknown Smear not performed Smear not read

12. Parasite density : _____%

13. Antimalarial drugs administered prior to starting IV artesunate:

- Coartem Malarone Quinine+Doxycycline Quinine+Clindamycin Mefloquine
 Other, specify _____

Participant ID:

14. Admission laboratory results:

Lab	Value	Unit	Date drawn (mm/dd/yyyy)	Time drawn (hh:mm)
Hemoglobin		g/dL	___/___/___	___:___
Hematocrit		%	___/___/___	___:___
Platelets		/uL	___/___/___	___:___
White blood cells		/uL	___/___/___	___:___
Sodium		mmol/L	___/___/___	___:___
Potassium		mmol/L	___/___/___	___:___
Chloride		mEq/L	___/___/___	___:___
Bicarbonate		mmol/L	___/___/___	___:___
BUN		mg/dL	___/___/___	___:___
Creatinine		mg/dL	___/___/___	___:___
Glucose		mg/dL	___/___/___	___:___
Lactate dehydrogenase (LDH)		U/L	___/___/___	___:___
AST		U/L	___/___/___	___:___
ALT		U/L	___/___/___	___:___
Bilirubin, total		mg/dL	___/___/___	___:___

15. Physician's Name _____

16. Physician's Phone

i. Office: _____

ii. Pager: _____

iii. Cellular: _____

iv. Email Address: _____

17. Hospital Name _____

18. Hospital Address _____

Hospital Phone: _____

APPENDIX II

Participant ID:

Treatment Plan

- Determine patient's dose of artesunate:

Adults and children \geq 20 kg:

Artesunate 2.4 mg/kg at 0 hour, 12 hours, and 24 hours

Children < 20 kg:

Artesunate 3.0 mg/kg at 0 hour, 12 hours, and 24 hours

- Reconstitute artesunate

The formulation of artesunate consists of two parts. Part A is a vial filled with base artesunate, the active component; Part B (diluent) is a vial filled with phosphate solution used to dissolve the artesunate in Part A just prior to administration.

Specifically, 11 ml of diluent will be withdrawn from the diluent vial (Part B) and injected into the artesunate vial (110 mg of artesunate) (Part A). This mixture will be gently swirled for 5 to 6 minutes (resulting in a concentration of 10 mg/ml) and will be administered within 1 hour.

Artesunate for injection

Manufactured by SRI International, Menlo Park, CA, US

Lot #: 090403-A, produced in September 2003

Phosphate Buffer USP (diluent), 0.3 Molar, pH 8.1

Manufactured by SRI International, Menlo Park, CA US

Lot #: 090403-B, produced in September 2003

- Administer the reconstituted drug intravenously by injection into an established intravenous line or needle over 1-2 minutes through the 0.8-micron hydrophilic polyethersulfone filter syringe provided in the packet.

- Watch patient for 30 minutes. Observe any development of allergic symptoms such as itching, redness, swelling, shortness of breath, chest pain, or watery eyes.

If patient develops any allergic reaction, manage symptoms accordingly and discontinue treatment.

- If the patient experiences any Serious Adverse Events (SAEs), report them to CDC within 24 hours by telephone.

- Complete the Adverse Events Report Form. If the patient experiences any Adverse Events regardless of potential relationship to artesunate, it must be reported within 10 days of the AE.

Follow-on Oral Treatment

The follow-on oral drug should be initiated on the last day of artesunate treatment, at least 4 hours after the IV dose of artesunate. Use ONE of the following, by decreasing order of preference:

Participant ID:

1. Artemether-lumefantrine (Coartem) (first choice)

The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 oral dose twice daily for the following 2 days (a total of 6 doses over 3 days).

1 tablet = 20mg artemether/ 120 mg lumefantrine

5 - <15 kg: 1 tablet per dose; initial dose then second dose at 8 hours, then 1 dose bid for the following 2 days

15 - <25 kg: 2 tablets per dose; initial dose then second dose at 8 hours, then 1 dose bid for the following 2 days

25 - <35 kg: 3 tablets per dose; initial dose then second dose at 8 hours, then 1 dose bid for the following 2 days

≥35 kg: 4 tablets per dose; initial dose then second dose at 8 hours, then 1 dose bid for the following 2 days

Note: Artemether-lumefantrine can be used in second and third trimesters of pregnancy. It can be used in first trimester of pregnancy if no other drug options are available. It is not recommended in infants weighing <5 kg.

2. Atovaquone-proguanil (Malarone) (second choice)

Adults: Tabs of 250/100 mg: four tabs po daily for 3 consecutive days

Children: Tabs of 62.5/25 mg (peds tabs) or 250/100 mg (adult tabs) po at the following weight-based doses:

5 – 8 kg: 2 peds tabs po daily for 3 consecutive days

9 – 10 kg: 3 peds tabs po daily for 3 consecutive days

11 – 20 kg: 1 adult tab po daily for 3 consecutive days

21 – 30 kg: 2 adult tabs po daily for 3 consecutive days

31 – 40 kg: 3 adult tabs po daily for 3 consecutive days

> 40 kg: 4 adult tabs po daily for 3 consecutive days

Note: Atovaquone-proguanil is not recommended for infants under 5 kg.

3. Quinine + doxycycline (or clindamycin for children under 8 years or pregnant women) (third choice; for patients who cannot take artemether-lumefantrine or atovaquone-proguanil)

Adults (excluding pregnant women: 100 mg doxycycline po bid for 7 days

Children (8 years or older): 4 mg/kg/day doxycycline divided bid for 7 days

Children under 8 years or pregnant women: instead of doxycycline, administer clindamycin 20 mg base/kg/day divided tid for 7 days

4. Mefloquine (fourth choice, for patients who cannot take atovaquone-proguanil, doxycycline, and clindamycin)

Adults: Initial dose of 750 mg salt po followed by 500 mg salt 6-12 hours after initial dose

Children: Initial dose of 15 mg salt/kg po followed by 10 mg salt/kg po given 6-12 hours after initial dose

Patients still not tolerating oral medications after 24 hours of IV artesunate:

If, after 24 hours of treatment with IV artesunate, the patient still cannot tolerate oral medications, several treatment options are available, depending on the patient's clinical and parasitological status. The most suitable course of treatment should be selected by the attending clinicians in consultation with CDC. Potential options include:

1. Continue the IV artesunate, not to exceed a total course of 7 days
2. Switch to treatment with IV doxycycline (7 days) or IV clindamycin (7 days).

(these regimens are described more in detail on the CDC website https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html)

As soon as the patient can tolerate oral medications, switch to an appropriate oral follow-on treatment.

Participant ID:

Day 0 Artesunate Dosing

1. Dosing date (mm/dd/yyyy): _____ / _____ / _____
2. Participant's weight: _____ kg
3. Dose ordered: _____ mg
4. Dosing start time (hh:mm): ____:____ ; Dosing stop time (hh:mm): ____:____
5. Did participant receive the entire dose?
 Yes
 No; Total amount received: _____ ml
Record the reason the full dose was not received: _____

12 hour dose

Was participant dosed? Yes (complete below) No; reason not dosed: _____
(section is complete)

1. Dosing date (mm/dd/yyyy): _____ / _____ / _____
2. Dose ordered: _____ mg
3. Dosing start time (hh:mm): ____:____ ; Dosing stop time (hh:mm): ____:____
4. Did participant receive the entire dose?
 Yes
 No; Total amount received: _____ ml
Record the reason the full dose was not received: _____

24 hour dose

Was participant dosed? Yes (complete below) No; reason not dosed: _____
(section is complete)

1. Dosing date (mm/dd/yyyy): _____ / _____ / _____
2. Dose ordered _____ mg
3. Dosing start time (hh:mm): ____:____ ; Dosing stop time (hh:mm): ____:____
4. Did participant receive the entire dose?
 Yes
 No; Total amount received: _____ ml
Record the reason the full dose was not received: _____

Were additional doses of artesunate needed after 3 doses?

Yes

1. If yes, why? still unable to take oral medication parasitemia >1%

Other, specify, _____

2. Indicate the additional IV artesunate doses administered by completing table below:

Additional Dose #	Dose (mg) Administered	Date (mm/dd/yyyy)	Full Dose Administered (Yes/No)	If No, Explain
4th		___/___/___		
5th		___/___/___		
6th		___/___/___		
7th		___/___/___		
8th		___/___/___		
9th		___/___/___		

No

Participant ID:

Follow-on dosing

1. Was the participant dosed sequentially with an oral agent?

Yes (*complete below*) No, reason not dosed: _____
(page is complete)

Check medication given (*check one*): Coartem Malarone Doxycycline Mefloquine
 Clindamycin (children under 8 years or pregnant women)

Complete dosing information in table below. Cross through, initial and date any rows not needed.

Date of dosing (mm/dd/yyyy)	Time of dosing (hh:mm)
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _
_ _ / _ _ / _ _ _ _	_ _ : _ _

Participant ID:

1. Adjunctive and supportive treatments used (check all that apply):

- Blood transfusion
- Exchange transfusion
- Intubation
- Dialysis
- Vasopressors
- Other (specify):

Malaria Microscopy

Record all smears for the participant in the tables below. Cross through, initial and date any portion of the page not needed.

If a smear was performed, do not leave any rows of the table blank - Record '0' for those smears where parasites are not present.

Provide parasitemia levels until 0% parasitemia is met; use additional paper or space as needed.

Date drawn: / / ; Time drawn: :
mm dd yyyy hh mm

Parasite Species	% Parasitemia
<i>P. falciparum</i>	
<i>P. vivax</i>	
<i>P. ovale</i>	
<i>P. malariae</i>	

Date drawn: / / ; Time drawn: :
mm dd yyyy hh mm

Parasite Species	% Parasitemia
<i>P. falciparum</i>	
<i>P. vivax</i>	
<i>P. ovale</i>	
<i>P. malariae</i>	

Date drawn: / / ; Time drawn: :
mm dd yyyy hh mm

Parasite Species	% Parasitemia
<i>P. falciparum</i>	
<i>P. vivax</i>	
<i>P. ovale</i>	
<i>P. malariae</i>	

Participant ID:

End of Trial

1 End date* (mm/dd/yyyy): ____/____/____

2 Did subject complete treatment? Yes No (complete below)

Check **one primary** reason the participant did not complete the treatment:

- Adverse event (AE)/Serious adverse event (SAE)
- Death
- Withdrawal of consent (check one) Investigator request Participant request
- Lost to follow-up
- Other; specify reason: _____

*Complete 'End date' as follows:

If participant

Completed through day XX
Discontinued due to AE/SAE
Died
Withdrawal of consent
Lost to follow-up
Other

Record date as

Day XX visit date
Date it was determined to discontinue due to AE/SAE
Date of death
Date of withdrawal (either investigator request or subject request)
Date of last contact with subject (telephone call, office visit, etc.)
Date of 'Other' event

I have reviewed all case report forms and attest that the data contained in them is accurate and complete.

Clinician's Signature

_____/_____/_____
Date Signed (mm/dd/yyyy)

APPENDIX III

Participant ID:

Adverse Event Reporting (make multiple copies of this page if required)

Record Serious Adverse Events (AE) reported/observed for the participant

OR Check box below if NO adverse events experienced by patient.

(form is complete)

For all AEs: Fill out this form and fax or email it to the CDC Malaria Branch [fax: (404)-471-8035 or 404-471-2555; email: why6@cdc.gov or ktan@cdc.gov] or mail it to the CDC Malaria Branch (Address: 1600 Clifton Road NE, MS A-06, Atlanta, GA 30333) within 10 calendar days from the AE.

If serious adverse events (SAEs) occur: Notify CDC **within 24 hours** by telephone. Call the CDC Malaria Hotline at 770-488-7788 from 9:00am to 5:00 pm Eastern time; after hours call the CDC Emergency Operations Center at 770-488-7100. Ask to speak with the malaria clinician on call.

Adverse event name & description (see supplemental form below if hemolysis)		
Severity		<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe
Was this an SAE?	<input type="checkbox"/> No <input type="checkbox"/> Yes	If yes, specify: <input type="checkbox"/> ₁ Death <input type="checkbox"/> ₂ Life-threatening <input type="checkbox"/> ₃ Persistent or symptomatic disability or incapacity <input type="checkbox"/> ₄ Hospitalization or prolongation of hospitalization <input type="checkbox"/> ₅ Congenital anomaly or birth defect <input type="checkbox"/> ₆ Other important medical event
Date and Time of Onset		Date: _____ Time: _____ MM/DD/YYYY HH:MM
Date and Time of Resolution		Date: _____ Time: _____ MM/DD/YYYY HH:MM
Relationship to:	Artesunate	<input type="checkbox"/> Not Related <input type="checkbox"/> Unlikely <input type="checkbox"/> Possible <input type="checkbox"/> Probable <input type="checkbox"/> Definite
	Follow-on drug	<input type="checkbox"/> Not Related <input type="checkbox"/> Unlikely <input type="checkbox"/> Possible <input type="checkbox"/> Probable <input type="checkbox"/> Definite
Action taken with artesunate due to AE		<input type="checkbox"/> None <input type="checkbox"/> Dosing changed: describe _____ <input type="checkbox"/> Dosing temporarily interrupted: describe _____ <input type="checkbox"/> Artesunate permanently discontinued
Did AE require treatment?		<input type="checkbox"/> No <input type="checkbox"/> Yes
Outcome		<input type="checkbox"/> Recovered <input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved with residual effects <input type="checkbox"/> Death
Concurrent medications at time of event		List all with start and stop dates (mm/dd/yyyy):
Notes		

Supplemental Adverse Event Form for Delayed Hemolysis

Weekly laboratory evaluation for up to 4 weeks after treatment should be conducted to assess for post-artesunate delayed hemolysis. Labs should include hemoglobin, reticulocyte count, haptoglobin, lactate dehydrogenase (LDH), and total bilirubin.

If hemolysis occurs **7-28 days** after treatment with IV artesunate, provide the following laboratory values at hemoglobin nadir:

Lab	Value	Unit	Date drawn (mm/dd/yyyy)	Time drawn (hh:mm)
Hemoglobin		g/dL	___ / ___ / ___	___ : ___
Reticulocytes		%	___ / ___ / ___	___ : ___
Haptoglobin		mg/dL	___ / ___ / ___	___ : ___
Lactate dehydrogenase (LDH)		U/L	___ / ___ / ___	___ : ___
Bilirubin, total		mg/dL	___ / ___ / ___	___ : ___

Appendix IV

List of CDC Quarantine Stations that stock Artesunate

Artesunate will be stored at the CDC Drug Service at CDC Headquarters in Atlanta, as well as in CDC Quarantine Stations. Current Quarantine Stations that stock artesunate are listed below, with their jurisdiction for artesunate delivery.

1. CDC Atlanta Quarantine Station
Hartsfield International Airport
Jurisdiction: Georgia, Alabama, Mississippi, North Carolina, South Carolina, and Tennessee.
2. CDC Chicago Quarantine Station
O'Hare International Airport
Jurisdiction: Illinois, Indiana, Iowa, Nebraska, South Dakota, North Dakota, Minnesota, Michigan, Ohio, Kentucky, and Wisconsin.
3. CDC Honolulu Quarantine Station
Honolulu International Airport
Jurisdiction: Hawaii, Guam, and Pacific Trust Territories.
4. CDC Houston Quarantine Station
George Bush Intercontinental Airport (IAH)
Jurisdiction: Texas, New Mexico, Kansas, Missouri, Arkansas, Louisiana, and Oklahoma.
5. CDC Los Angeles Quarantine Station
Tom Bradley International Airport
Jurisdiction: Southern California (Los Angeles, Orange, San Bernardino, Riverside, Ventura, Santa Barbara, and San Luis Obispo counties), Colorado, and Arizona.
6. CDC Miami Quarantine Station
Miami International Airport
Jurisdiction: Florida, Puerto Rico and the Virgin Islands.
7. CDC New York Quarantine Station
JFK International Airport
Jurisdiction: New York, Maine, New Hampshire, Massachusetts, Rhode Island, Connecticut, Pennsylvania, New Jersey, Delaware, Maryland, and parts of Virginia, West Virginia, and Vermont
8. CDC San Francisco Quarantine Station
San Francisco International Airport
Jurisdiction: Central and Northern California (46 counties), Nevada, Utah, and Wyoming.

9. CDC Seattle Quarantine Station
Seattle-Tacoma International Airport
Jurisdiction: Washington, Idaho, Montana, Oregon, and Alaska.

10. CDC Washington D.C. Quarantine Station
Dulles International Airport
Jurisdiction: Washington DC, Maryland, and parts of Virginia

Appendix V

PARTICIPANT CONSENT / PARENTAL PERMISSION FORM

Flesch-Kincaid 7.6 (without title and signature block)

You or your child are being asked to take part in this treatment program because you or your child have severe malaria. Severe malaria is the most serious form of malaria, which one gets through the bite of an infected mosquito. Usually, this type of bite happens while traveling in a part of the world that has the malaria parasite. Severe malaria can lead to many problems including coma, kidney and lung trouble, anemia (low red blood cells), and death.

This treatment program is sponsored by the Centers for Disease Control and Prevention (CDC). This program will use the drug artesunate to treat your severe malaria. Artesunate is an investigational drug. This means that artesunate has not been approved by the Food and Drug Administration (FDA) to treat malaria in the United States (U.S.). You or your child are being asked to take artesunate because you or your child have severe malaria.

Intravenous (IV) (by vein) artesunate has been used in many other parts of the world to treat severe malaria. Before deciding whether to take part, we want you or your child to know about the program.

This is a consent form. It gives information about this program. The program staff will talk with you or your child about this information. You or your child are free to ask questions at any time. Taking part in this program is voluntary. You or your child may leave this program at any time. If you or your child decide not to take part in or to stop this program, it will not affect the medical care you or your child would normally get. If you or your child agree to take part in this program, you will be asked to sign this consent form. You will get a copy to keep.

WHAT WILL HAPPEN TO ME?

We will take blood for tests to count the number of parasites (germs) in your or your child's blood at the start of treatment and then every 12 hours.

We will ask you or your child about drugs you or your child are taking, any allergies, and your or your child's health.

We will give you or your child artesunate by vein. Then we will watch you or your child for about 30 minutes to make sure that you or your child don't have an allergic reaction to artesunate. If any allergic reactions or other side effects are seen, you or your child will be treated. Costs for hospital and medical care will not be covered by the CDC and will need to be paid by you, your insurer, Medicare, or Medicaid.

We will give you or your child doses of artesunate by vein every day for 3 days. Then we will switch you or your child to another medicine that you or your child can take by mouth.

If we cannot make the switch from medicine by vein to medicine by mouth because you or your child cannot take medicines by mouth, we will continue giving you or your child medicines by vein as needed; but you or your child will not receive artesunate for more than 7 days.

HOW MANY PEOPLE WILL TAKE PART IN THIS TREATMENT PROGRAM?

We do not know how many people will need artesunate to treat severe malaria.

ARE THERE BENEFITS?

By taking artesunate, you or your child may be cured of severe malaria.

ARE THERE RISKS?

Most people do not have serious problems when they take artesunate. There are rare reports of people developing anemia (low red blood cells) up to one month after they take artesunate. There is a chance that you or your child will have side effects, including an allergic reaction. When we draw blood for tests, or when we inject drugs by vein, there is a chance that this may cause pain, bleeding, or bruises where the needle enters the skin. In rare cases, needle sticks may cause fainting or infection.

WHAT ARE THE OTHER CHOICES BESIDES THIS PROGRAM?

There are no other FDA-approved IV drugs available for severe malaria.

WHAT IF I AM PREGNANT?

We do not know enough about artesunate to be sure that it will not cause harm to pregnant women and their babies. However, one recent study that included 183 pregnant women with malaria found that artesunate did not seem to cause miscarriages or congenital malformations. Also, malaria in itself can be harmful to the pregnant woman and her baby. You and your doctor will have to weigh the risks and benefits of taking artesunate, for you and your baby, if you are pregnant.

WHAT ABOUT PRIVACY?

We will keep all information about you or your child as private as the law allows. People who work at CDC and FDA may look at your medical records. Your or your child's name and personal information will not be used or listed in reports or articles in magazines or journals. However, FDA rules say that CDC has to follow certain laws and rules to give this drug to you or your child. Your or your child's doctor has to give CDC a report about your or your child's response to treatment with artesunate. This is necessary because CDC has to report to FDA about the safety of artesunate. If more details about your or your child's treatment course are needed, your or your child's doctor might have to give CDC a copy of your or your child's medical records. Your or your child's doctor may contact you in the future to obtain follow up information that could be shared with CDC. FDA and the company that makes artesunate are allowed to look at CDC's files about participants treated with this drug. Also, CDC is allowed to give your or your child's name to public health or medical people who, for example, need to find out how you or your child got the infection and how to prevent other cases.

VOLUNTARY PARTICIPATION

It is your choice to take artesunate or for your child to be treated under this protocol.

- You may refuse or stop treatment at any time.

- You or your child will not lose any rights to get other health care by being in this program or by not being in this program.

WHAT IS THE COST OF THIS DRUG?

The drug will be given to you or your child free of charge. The other costs of the hospital and medical care are not covered by the CDC and will need to be paid by you, your or your child's insurer, Medicare, or Medicaid.

WHAT HAPPENS IF I AM HARMED?

If you are hurt from being in this program, treatment will be given by the medical staff at your or your child's hospital. CDC does not normally pay for harm done to you or your child as a result of being in a treatment program. Thus, you, your or your child's insurer, Medicare, or Medicaid will have to pay for any care that is needed. However, by signing this consent form and agreeing to be in this program, you or your child are not giving up any of your or your child's rights.

WHO CAN I CALL IF I HAVE PROBLEMS OR QUESTIONS?

If you have any questions about this program, you may talk with your doctor, Dr. _____ at the following phone number _____.

You may talk with the available CDC malaria doctor at either 770-488-7788 or 770-488-7100. If you feel that you or your child have been harmed please contact Dr. Francisca Abanyie-Bimbo (at 404-718-4775) or Dr. Kathrine Tan (at 404.718.4701) during normal business hours Monday to Friday, 9 am- 5 pm EST. If you have questions about your or your child's rights as a participant in this program, please contact CDC's Human Research Protection Office at (800)584-8814. Please leave a message that includes your name and telephone number, and refer to CDC protocol # 5032.

CONSENT STATEMENT

I have read the form or it has been read to me. I have been given a chance to ask questions and my questions have been answered. I agree to get or for my child to get intravenous artesunate to help treat severe malaria.

Print Participant/Parent Name: _____

Participant/Parent Signature: _____ Date: _____

Legally Authorized Representative Signature: _____ Date: _____

Witness Signature: _____ Date: _____

(If applicable) I have translated this form into the _____ language.

Translator's Signature: _____ Date: _____

NOTE: If participant is unable to sign, next of kin or legal guardian may sign.

NOTE: The participant will be offered a copy of the consent form.

NOTE: If signatures are obtained above, consent form is complete. No physician signature needed below.

If participant gives verbal consent, but is unable to sign and next of kin or legal guardian is not available, the patient should give his/her mark (either an "X" or a thumbprint), and the consenting physician should complete the following:

I, (Print Physician's Name) _____ certify that the above named participant has read this document or had it read to them, is unable to sign the document, and has verbally consented to participate. I further certify that a next of kin or a legal guardian who could sign for the participant is not readily available.

Physician's Signature: _____ Date: _____

IF OBTAINING INFORMED CONSENT IS NOT FEASIBLE:

In the event that obtaining informed consent is not feasible because the patient is unable to respond and make wishes known about artesunate treatment and no legal guardian or next of kin is present the following provides for the treating physician to make a clinical determination to treat with artesunate provided that the treating physician and an independent physician certifies to the following within 2 working days of treating the patient with artesunate:

1. Patient is confronted by a life-threatening situation necessitating the use of artesunate
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.
3. Time is not sufficient to obtain consent from the patient's legal representative.
4. There is no available alternative method of approved or generally recognized

therapy that provides an equal or greater likelihood of saving the life of the patient.

Document as such in the patient's medical record and ensure the patient or patient's legally authorized representative is made aware that investigational artesunate was administered.

Name & signature of treating physician who made the determination to administer artesunate to patient when informed consent could not be obtained:

_____	_____	_____
Name	Signature	Date

Name & signature of second physician, who is not otherwise participating in this treatment protocol, reviewing and evaluating decision to administer artesunate to patient:

_____	_____	_____
Name	Signature	Date

Return copy of this signed page to CDC

PARTICIPANT ID:

WRAIR (DOD)

APPENDIX VI INVESTIGATIONAL DRUG ACCOUNTABILITY AND RETURN FORM

A pharmacist should complete and return this form within 14 days of the patient completing treatment.

Form should be returned to the CDC Drug Service: drugservice@cdc.gov or fax (404) 639-3717

DRUG ACCOUNTABILITY:

of Artesunate drug/diluent Vials Received: ____ / ____

Date Received: ____ / ____ / ____

Lot # of drug/diluent: _____ / _____

of Artesunate drug/diluent Vials Used: ____ / ____

START Date: ____ / ____ / ____

END Date: ____ / ____ / ____

Final Balance of Artesunate drug/diluent Vials Remaining: ____ / ____

RETURN of UNUSED IV ARTESUNATE VIALS:

Unopened and unused IV artesunate and diluents should be returned to CDC Drug Service by *maintaining the cold chain* and shipping to following address for arrival on a weekday:

CDC DRUG SERVICE,
Mailstop D-09
1600 CLIFTON RD NE.
ATLANTA, GA 30329
Telephone: 404-639-3670

Please contact CDC Drug Service (404-639-3670 or drugservice@cdc.gov) to notify the staff of the return shipment of IV artesunate and provide shipment information (e.g., date of shipment, arrival date, courier, tracking #).

of Artesunate drug/diluent Vials Returned: ____ / ____

Date Returned: ____ / ____ / ____

**If unopened and unused IV artesunate and diluents cannot be returned, contact CDC Drug Service:*

404-639-3670 or drugservice@cdc.gov

Name of Pharmacist Responsible for Product Accountability: _____

Signature of Pharmacist Responsible for Product Accountability: _____