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PROGRAM CONTACT INFORMATION

Principal Investigators:
Francisca Abanyie-Bimbo, MD, MPH
Medical Epidemiologist, Domestic Response Unit
Division of Parasitic Diseases and Malaria
Centers for Disease Control and Prevention
1600 Clifton Road NE, MS H24-3
Atlanta, GA 30329-4027
Phone: 404.718.4775
Fax: 404.471.8035

Kathrine Tan, M.D. MPH
Chief, Domestic Response Unit
Division of Parasitic Diseases and Malaria
Centers for Disease Control and Prevention
1600 Clifton Road NE, MS H24-3
Atlanta, GA 30333
Phone: 404.718.4701
Fax: 404. 471-2555

Clinical Project Manager:
Francisca Abanyie-Bimbo, MD, MPH
Kathrine Tan, M.D., MPH

Medical Monitor:
Francisca Abanyie-Bimbo, MD, MPH
Kathrine Tan, M.D., MPH

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, is not approved by the FDA in the US. Since 2007, CDC has sponsored an expanded access Investigational New Drug (IND) program to make IV artesunate available for the treatment of severe malaria under an IND protocol with IV artesunate product produced by the Walter Reed Army Institute of Research (WRAIR). Due to the limited remaining stock of WRAIR-supplied product and the anticipated increase in need for IV artesunate with quinidine unavailability, CDC is also providing IV artesunate manufactured by Guilin Pharmaceutical Co., Ltd. (part of Fosun Pharma) for use under this IND protocol (CDC IRB Protocol # 7171). Guilin- manufactured IV artesunate is also sourced by the WHO for its recommended use of IV artesunate as the first-line treatment for severe malaria, and was used in large clinical trials that demonstrated increased safety and efficacy compared to IV quinine (Dondorp 2005 and Dondorp 2010). The release of IV artesunate under this IND protocol by CDC is upon receipt of physician-request for a patient with severe malaria. Treatment with IV artesunate should be followed by oral treatment with artemether-lumefantrine (Coartem™), atovaquone-proguanil (Malarone), doxycycline, clindamycin, or mefloquine to ensure maximal curative effect. Physicians who request and/or receive IV artesunate from CDC under this IND protocol are responsible for managing IV artesunate treatment and should 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. In 2016, there were an estimated 440,000 deaths caused by severe malaria, with the majority of deaths occurring in young children (WHO 2017). Sub-Saharan Africa continues to carry a disproportionately high share of the global malaria burden. 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*. Severe manifestations of disease have also been observed 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

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 parasiticidal 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 IV 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 US. In the US, severe malaria has historically been treated 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

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 IV 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 SEQUAMAT 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. falciparu*m malaria.

The evidence-based 2015 WHO Guidelines for Treatment of Malaria consider artemisinin derivatives to be the first-line drug for the treatment of severe malaria (WHO 2015).

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 0.12-00.24 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 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 ≥10% over baseline at least 7 days after initiation of parenteral artesunate treatment.

Five cases of delayed hemolytic anemia have been identified in the US after the use of WRAIR-supplied artesunate for the treatment of severe malaria under the CDC-sponsored IND program. 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 investigator investigators, Dr. Francisca Abanyie-Bimbo (404) 718-4775 or, Dr. Kathrine Tan at ktan@cdc.gov or (404) 718-4701.

4.4. Artesunate usage during pregnancy and in lactating women

Guilin's IV artesunate prescribing information (version dated 10/2018) states that artesunate has been associated with fetal toxicity during the first trimester of pregnancy in animal studies; however, limited clinical experience with artesunate use in the first trimester of pregnancy as well as clinical data from use in over 2,500 pregnant women treated with artesunate mostly in

the second and third trimesters do not indicate adverse effects on the pregnancy or fetus/newborn due to artesunate exposure. For lactating women, limited information indicates that low levels of dihydroartemisinin is found in breast milk. The drug levels are not expected to cause any adverse effects in breastfed infants, nor does it protect the infant from malaria. Below is a summary of the information on artesunate use and pregnancy from literature and studies conducted by 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 (WHO 2015).

5.0 ARTESUNATE: PRODUCT SOURCE AND DESCRIPTION

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 ≥ 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

Date Informed Consent form signed *(mm/dd/yyyy)*: ___/_____/____

Date of enrollment *(mm/dd/yyyy)*: ____/____/_____

Participant ID: ☐☐☐☐☐☐

Date drawn (*mm/dd/yyyy*): ____/____/_____; Time drawn (*hh:mm*):____:____

Parasite Species	% Parasitemia
P. falciparum	
P. vivax	
P. ovale	
P. malariae	

Laboratory Results

Record at least 1 set of laboratory results during or within 8 hours of completion of IV artesunate treatment. If labs are drawn on multiple days, select the lab values drawn closest to administration of the last dose.

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	___/___/_____	____:____

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	**Record date as**
Completed through day XX	Day XX visit date
Discontinued due to AE/SAE	Date it was determined to discontinue due to AE/SAE
Died	Date of death
Withdrawal of consent	Date of withdrawal (either investigator request or subject request)
Lost to follow-up	Date of last contact with subject (telephone call, office visit, etc.)
Other	Date of 'Other' event

I have reviewed all case report forms and attest that the data contained in them are 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 Adverse Events (AE) reported/observed for the participant

OR ***Check box 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		☐Mild ☐Moderate ☐Severe
Was this an SAE?	☐ No ☐ Yes	**If yes, specify:** ☐ 1 Death ☐ 2 Life-threatening ☐ 3 Persistent or symptomatic disability or incapacity ☐ 4 Hospitalization or prolongation of hospitalization ☐ 5 Congenital anomaly or birth defect 6 Other important medical event
Date and Time of Onset		Date: _____ (MM/DD/YYYY) Time: _____ (HH:MM)
Date and Time of Resolution		Date: _____ (MM/DD/YYYY) Time: _____ (HH:MM)
Relationship to:	Artesunate	☐ Not Related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
	Follow-on drug	☐ Not Related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Action taken with artesunate due to AE		☐ None ☐ Dosing changed: describe _____ ☐ Dosing temporarily interrupted: describe _____ ☐ Artesunate permanently discontinued
Did AE require treatment?		☐No ☐ Yes
Outcome		☐ Recovered ☐ Ongoing ☐ Resolved with residual effects ☐ 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 Ph:
   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 D.C., Maryland, Virginia, and West 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 d e a t h .

This treatment program is sponsored by the Centers for Disease Control and Prevention (CDC). This program will use the drug artesunate to treat your or your child's 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 is 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?
Studies of about 2000 pregnancies exposed to artemisinins 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 # 7171

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: ☐☐☐☐☐☐ GUILIN (FOSUN)

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 Dose Kits Received: _____ **Date Received: : _____/____/____**

Lot # of product: _____

# of Dose Kits Used: _____ **Date(s) Used: START Date: _____/____/____**

END Date: ____/____/_____

# of Dose Kits Remaining: _____

RETURN of UNUSED IV ARTESUNATE VIALS:

Unopened and unused IV artesunate and diluents should be returned to CDC Drug Service by 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 Dose Kits 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: _____