

# Clinical investigation of in-vivo susceptibility of Plasmodium falciparum to artesunate in Western Cambodia (study 2)

<b>Submission date</b> 14/05/2008	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered
<b>Registration date</b> 16/05/2008	<b>Overall study status</b> Completed	<input type="checkbox"/> Protocol
<b>Last Edited</b> 19/06/2015	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
		<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

Not provided at time of registration

## Contact information

### Type(s)

Scientific

### Contact name

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### Contact details

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## Additional identifiers

### Protocol serial number

BKMAL0801; 077166

## Study information

## **Scientific Title**

Clinical investigation of in-vivo susceptibility of Plasmodium falciparum to artesunate in Western Cambodia (study 2)

## **Study objectives**

There are worrying signs from Western Cambodia that parasitological responses to artesunate and artemether containing treatment regimens for uncomplicated falciparum malaria are slower than elsewhere in the world. Both delayed parasite clearance and unusually high failure rates with artesunate-mefloquine and artemether-lumefantrine have been reported. Although occasional poor responses to artesunate have been described previously the current reports suggest a consistent problem.

In pooled data from 12,553 patients receiving artemisinin derivatives, 17% had parasite clearance times (PCTs) over 48 hours and 5% had PCTs over 72 hours. As the rate of parasite clearance is a good pharmacodynamic measure of efficacy of the artemisinin related compounds, slow parasite clearance could indicate the emergence of significant resistance. These antimalarials are central to current treatment strategies, and so spread of significant resistance outside this area would be a disaster. Radical containment measures might be needed. In this context there is an urgent need to proceed quickly to investigate the level of resistance to artemisinin derivatives in Western Cambodia to provide a definitive assessment so that if necessary containment plans can be developed in 2007/2008.

A group of malaria investigators from Cambodia and Thailand have joined together to address this urgent question as quickly and effectively as possible. The trial described here proposes to assess the current recommended doses given in the normal way, and if necessary a higher dose of artesunate. There is no known dose related toxicity with artesunate, and doses up to 10 mg/kg /day have been given (by us) without any adverse effects. The two features of this study which differ from normal studies in uncomplicated malaria are the repeated blood sampling and the seven-day in-patient stay. If responses to artesunate are poor it is essential to have characterised the blood concentration profile as well as the parasitological response to differentiate resistance from abnormal pharmacokinetics.

As of 22/02/2010 this record has been updated to include an extended sample size due to the inclusion of a site in Thailand as well as the original site in Cambodia. The target number of participants has been updated to reflect this; the initial target number of participants was 40 (planned end of recruitment = 31/12/2008). The overall trial end date was also extended; the initial overall trial end date was 31/03/2009.

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

1. Oxford Tropical Medicine Research Ethics Committee (sponsor ethics approval), 13/12/2007, ref: OXTREC [015/07]
2. National Ethics Committee for Health Research (Cambodia), 07/12/2007, for the site: Pailin Hospital

## **Study design**

Multicentre randomised controlled trial

## **Primary study design**

Interventional

## Study type(s)

Treatment

## Health condition(s) or problem(s) studied

Acute falciparum malaria

## Interventions

Current interventions as of 22/02/2010:

Arm 1 (N = 40): receive artesunate alone at a dose of 6 mg/kg/day for seven days

Arm 2 (N = 40): receive artesunate alone at a dose of 6 mg/kg/day in two divided doses for seven days

Arm 3 (N = 40): receive artesunate at a dose of 8 mg/kg/day for three days, plus mefloquine at a dose of 15 mg/kg on day three and 10 mg/kg on day four

Arm 4 (N = 40): receive artesunate at a dose of 8 mg/kg/day in two divided doses for three days, plus mefloquine at a dose of 15 mg/kg on day three and 10 mg/kg on day four

Follow up duration for all arms: 63 days

Initial information at time of registration:

Arm 1 (N = 10): receive artesunate alone at a dose of 6 mg/kg/day for seven days

Arm 2 (N = 10): receive artesunate alone at a dose of 6 mg/kg/day in two divided doses for seven days

Arm 3 (N = 10): receive artesunate at a dose of 8 mg/kg/day for three days, plus mefloquine at a dose of 15 mg/kg on day three and 10 mg/kg on day four

Arm 4 (N = 10): receive artesunate at a dose of 8 mg/kg/day in two divided doses for three days, plus mefloquine at a dose of 15 mg/kg on day three and 10 mg/kg on day four

Follow up duration for all arms: 63 days

## Intervention Type

Drug

## Phase

Not Applicable

## Drug/device/biological/vaccine name(s)

Artesunate, mefloquine

## Primary outcome(s)

Parasite clearance times in relation to artesunate/dihydroartemisinin (DHA) plasma concentration (PK/PD) (time point: 63 days).

## Key secondary outcome(s)

1. Cure rates (time point: 63 days)
2. In vitro sensitivity of *P. falciparum* to artesunate measured prior to treatment (time point not applicable)
3. Molecular markers of drug resistance measured prior to treatment (time point not applicable)

## Completion date

01/12/2010

## Eligibility

### Key inclusion criteria

Children greater than 6 years old and adults (either sex) presenting with acute falciparum malaria will be eligible for this study provided that:

1. They or their parents/guardians give fully informed consent
2. They have not received antimalarial drugs in the previous 48 hours
3. Plasmodium falciparum parasitaemia exceeds 10,000 /uL
4. They agree to seven days of hospitalisation

### Participant type(s)

Patient

### Healthy volunteers allowed

No

### Age group

Mixed

### Sex

All

### Key exclusion criteria

1. Pregnancy
2. Microscopy indicates a mixed infection
3. History of allergy to artesunate or mefloquine

### Date of first enrolment

01/04/2008

### Date of final enrolment

31/10/2010

## Locations

### Countries of recruitment

Cambodia

Thailand

### Study participating centre

Mahidol-Oxford Research Unit

Bangkok

Thailand

10400

# Sponsor information

## Organisation

University of Oxford (UK)

## ROR

<https://ror.org/052gg0110>

## Funder(s)

### Funder type

Charity

### Funder Name

Wellcome Trust (UK) (grant ref: 077166)

### Alternative Name(s)

### Funding Body Type

Private sector organisation

### Funding Body Subtype

International organizations

### Location

United Kingdom

### Funder Name

Bill and Melinda Gates Foundation (USA) (grant ref: 48821)

### Alternative Name(s)

Bill & Melinda Gates Foundation, Gates Foundation, Gates Learning Foundation, William H. Gates Foundation, BMGF, B&MGF, GF

### Funding Body Type

Government organisation

### Funding Body Subtype

Trusts, charities, foundations (both public and private)

### Location

United States of America

# Results and Publications

## Individual participant data (IPD) sharing plan

### IPD sharing plan summary

#### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results	01/05/2010		Yes	No
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes