

**TCTR ID : TCTR20170830002**

**Overall Recruitment Status : Completed (Has Results)**

**OTHER ID :**

**Prospective registration**  
**This protocol was registered before enrollment of the first participant.**

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**Tracking Information**

First Submitted Date : 30 August 2017  
First Posted Date : 30 August 2017  
Last Update Posted Date : 17 March 2023

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**Title**

Public Title : Assessing the tolerability of a potentially safer radical curative regimen of primaquine in healthy volunteers with glucose 6 phosphate dehydrogenase deficiency in Thailand  
Acronym : PQ Challenge  
Scientific Title : Assessing the tolerability of a potentially safer radical curative regimen of primaquine in healthy volunteers with glucose 6 phosphate dehydrogenase deficiency in Thailand  
Sponsor ID/ IRB ID/ EC ID : BAKMAL1604  
Registration Site : Thai Clinical Trials Registry  
URL : <https://www.thaiclinicaltrials.org/show/TCTR20170830002>  
Secondary ID : No Secondary ID

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**Ethics Review**

1. Board Approval : Submitted, approved  
Approval Number : TMEC 16-106  
Date of Approval : 29 June 2017  
Board Name : Ethics Committee Faculty of Tropical Medicine  
Board Affiliation : Mahidol University  
Board Contact : Business Phone : 6623549100 Ext. 1349  
Business Email : tmectropmed@mahidol.ac.th  
Business Address : 420/6 Ratchawithi Rd., Ratchathewi, Bangkok 10400 Thailand

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**Sponsor**

Source(s) of Monetary or Material Supports : UK MRC (MR/R015252/1) & Wellcome Trust  
Study Primary Sponsor : University of Oxford  
Responsible Party : Name/Official Title : Dr. Bob Taylor  
Organization : Mahidol Oxford Tropical Medicine Research unit  
Phone : 6622036333 Ext. 6373  
Email : bob@tropmedres.ac  
Study Secondary Sponsor : No Study Secondary Sponsor

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**Protocol Synopsis**

Protocol Synopsis : To advance vivax control and elimination, a primaquine regimen in G6PD deficient patients is needed that is safe and will not produce severe haemolysis and could be deployed widely without testing for G6PDd. These considerations underlie the rationale of the study. The study aim is to determine the tolerability of different regimens of ascending dose primaquine under carefully controlled conditions to produce a slow burn haemolysis while simultaneously delivering sufficient primaquine that would be effective as radical cure in P. vivax. This is both a proof-of-concept study and also a regimen optimisation study to characterise the dose response relationship of primaquine and haemolysis. We also performed a single dose challenge study of 45 mg.

**URL not available**

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**Health Conditions**

Health Condition(s) or Problem(s) Studied : Malaria Primaquine radical cure  
Keywords : glucose 6 phosphate dehydrogenase deficiency

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**Eligibility**

Inclusion Criteria : 1. Male aged between the age of 18 and 65 years  
2. Healthy as judged by the examining physician  
3. Hb  $\geq$  11 g/dL  
4. G6PD activity  $<$  30% of the population median of 11.5 U/g Hb  
5. Written informed consent provided by the volunteer. Witnessed consent is required, if the individual cannot read or write.  
6. Willing to participate in this study

Gender : Male

Age Limit : Minimum : 18 Years Maximum : 65 Years

Exclusion Criteria : 1. BMI  $\geq$  35  
2. G6PD Mediterranean variant  
3. Known to have any clinically significant disease or to have a clinically significant disease or disorder discovered by the investigator requiring treatment or further investigation  
4. Malaria or other febrile illness (e.g. viral hepatitis, typhoid fever) in the previous month that could result in haemolysis in G6PDd  
5. Positive blood film for malaria (asexual or sexual parasites)  
6. History of haemolysis not related to primaquine in the past 8 weeks  
7. Being rhesus negative  
8. Received a blood transfusion in the past 3 months  
9. Subject who has donated more than 300 mL of whole blood within the previous 3 months  
10. Taking or taken within the past 3 weeks any herbal medicine  
11. Taking or taken within the past 3 weeks any drug known to cause haemolysis in G6PD deficiency  
12. AST and ALT and LDH  $>$  1.5 times the upper limit of normal (ULN)  
13. A serum creatinine above the upper limit of normal ( $>$ 1.2 mg/dL) and an eGFR  $<$  70 mL/min/1.73m<sup>2</sup> (the eGFR for males is calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:  
13.1  $eGFR = 141 \times \min(Scr/k, 1)^{\text{power } \alpha} \times \max(Scr/k, 1)^{\text{power } -1.209} \times 0.993^{\text{power Age}}$   
13.2 where Scr is serum creatinine,  $k = 0.9$  for males,  $\alpha = -0.411$  for males  
13.3 min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1)  
13.4 the eGFR can be calculated online: [https://qxmd.com/calculate/calculator\\_251/egfr-using-ckd-epi](https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi))  
14. Urine analysis (UA) reveals the chronic renal disease defined as RBC  $\geq$  5 and/or Proteinuria; trace or above  
15. Conjugated bilirubin  $>$  1.5 x ULN  
16. Unconjugated bilirubin  $>$  1.5 x ULN  
17. Methaemoglobin level  $>$  5% determined by oximetry  
18. Allergic to primaquine  
19. Have taken part in research involving an investigational drug within the past 8 weeks.  
20. Subject who, in the opinion of the investigator, have a risk of non-compliance with study procedures

Accept Healthy Volunteers : Yes

## Status

Overall Recruitment Status : Completed

Key Trial Dates	Study Start Date (First enrollment) : 21 November 2018	Indicate Type : Actual
	Completion Date (Last subject, Last visit) : 28 October 2020	Indicate Type : Actual
	Study Completion Date : 01 August 2022	Indicate Type : Actual

## Design

Study Type : Interventional  
Primary Purpose : Treatment  
Study Phase : Phase 2  
Intervention Model : Single arm  
Number of Arms : 1  
Masking : Open Label  
Allocation : No Data  
Control : N/A  
Study Endpoint Classification : Safety/Efficacy Study  
Sample size  
Planned sample size : 30  
Actual sample size at study completion : 24  
Intervention Arm 1

Intervention name : Healthy volunteer with proven G6PD deficiency  
Intervention Type : Experimental  
Intervention Classification : Drug  
Intervention Description : Primaquine daily dose starting with 1) 7.5 mg 5 days, 2) 15 mg 5 days, 3) 22.5 mg 5 days, and 4) 30 mg 5 days

## Outcome

### Primary Outcome

1. Outcome Name : safety and tolerability of a 20 day, ascending dose of primaquine in healthy volunteers with G6PD de  
Metric / Method of measurement : The proportion of subjects able to complete the study without having their primaquine stopped  
Time point : 1 year

### Secondary Outcome

1. Outcome Name : To determine markers of haemolysis over time  
Metric / Method of measurement : Validation of within-host model predictions of heamoglobin and reticulocyte dynamics over time  
Time point : 1 year

2. Outcome Name : To determine markers of haemolysis over time  
Metric / Method of measurement : Factors affecting Hb changes over time  
Time point : 1 year

3. Outcome Name : To determine markers of haemolysis over time  
Metric / Method of measurement : Time to nadir Hb concentration  
Time point : 1 year

4. Outcome Name : To determine markers of haemolysis over time  
Metric / Method of measurement : Nadir Hb concentration  
Time point : 1 year

5. Outcome Name : To determine markers of haemolysis over time  
Metric / Method of measurement : absolute and fractional fall in Hb on day of nadir Hb vs. baseline  
Time point : 1 year

6. Outcome Name : Pharmacokinetic (PK) properties of primaquine (PQ) and carboxyPQ  
Metric / Method of measurement : Pharmacokinetic (PK) properties of primaquine (PQ) and carboxyPQ  
Time point : 1 year

7. Outcome Name : G6PD enzyme activity and genotype and the presence of other inherited blood disorders  
Metric / Method of measurement : G6PD phenotype  
Time point : 1 year

8. Outcome Name : G6PD enzyme activity and genotype and the presence of other inherited blood disorders  
Metric / Method of measurement : G6PD genotype  
Time point : 1 year

9. Outcome Name : Rates of acute kidney injury  
Metric / Method of measurement : incidence of grade 3 & 4 clinical adverse events  
Time point : 1 year

10. Outcome Name : Rates of acute kidney injury  
Metric / Method of measurement : incidence of laboratory adverse events  
Time point : 1 year

11. Outcome Name : To determine markers of haemolysis over time  
Metric / Method of measurement : changes in biochemical markers of haemolysis over time  
Time point : 1 year

12. Outcome Name : Primaquine metabolite activity on in vitro cultured Plasmodium gametocytes  
Metric / Method of measurement : Primaquine metabolite  
Time point : 1 year

## Location

### Section A : Central Contact

Central Contact	First Name : Bob	Middle Name :	Last Name : Taylor
	Degree : MD	Phone : 6622036333 Ext. : 6373	Email : bob@tropmedres.ac
Central Contact Backup	First Name : Podjane	Middle Name :	Lastname : Jittmala
	Degree : MD	Phone : 6623548333 Ext. : 2404	Email : podjane@tropmedres.ac

#### Section B Facility Information and Contact

- Site Name : The PK ward at the Faculty of Tropical Medicine, Mahidol university  
City : Bangkok State/Province : Bangkok Postal Code : 10400  
Country : Thailand Recruitment Status : Completed

<b>Facility Contact</b>	First Name : Sasithon	Middle Name :	Last Name : Pukrittayakamee
	Degree : MD	Phone : 6623548333 Ext. : 2404	Email : yon@tropmedres.ac

<b>Facility Contact Backup</b>	First Name : Podjane	Middle Name :	Last Name : Jittmala
	Degree : MD	Phone : 6623548333 Ext. : 2404	Email : podjane@tropmedres.ac

<b>Investigator Name</b>	First Name : Sasithon	Middle Name :	Last Name : Pukrittayakamee
	Degree : MD	Role : Site Sub-Investigator	

- Site Name : The Shoklo Malaria Research unit, Maesot (SMRU)  
City : Mae Sot State/Province : Tak Postal Code : 63110  
Country : Thailand Recruitment Status : Completed

<b>Facility Contact</b>	First Name : Cindy	Middle Name :	Last Name : Chu
	Degree : MD	Phone : 6655545021 Ext. : No Data	Email : cindy@tropmedres.ac

<b>Facility Contact Backup</b>	First Name : Germana	Middle Name :	Last Name : Bancone
	Degree :	Phone : 6655545021 Ext. : No Data	Email : Germana@tropmedres.ac

<b>Investigator Name</b>	First Name : Cindy	Middle Name :	Last Name : Chu
	Degree : MD	Role : Site Sub-Investigator	

#### Section C : Contact for Public Queries (Responsible Person)

First Name : Nick	Middle Name :	Last Name : White
Degree : MD, Prof	Phone : 6622036333 Ext. : 6301	Email : nickw@tropmedres.ac
Postal Address : 420/6 Rajvithi road, Rajthevee		
State/Province : Bangkok	Postal Code : 10400	
Country : Thailand	Official Role : Study Principal Investigator	
Organization Affiliation : Mahidol Oxford Tropical Medicine Research unit		

#### Section D : Contact for Scientific Queries (Responsible Person)

First Name : Nick	Middle Name :	Last Name : White
Degree : MD, Prof	Phone : 6622036333 Ext. : 6301	Email : nickw@tropmedres.ac
Postal Address : 420/6 Rajvithi road, Rajthevee		
State/Province : Bangkok	Postal Code : 10400	
Country : Thailand	Official Role : Study Principal Investigator	
Organization Affiliation : Mahidol Oxford Tropical Medicine Research unit		

#### Summary Results

Date of posting of results summaries : 25 February 2023

Date of first journal publication of results : Not yet published

Baseline Characteristics : Ascendig dose only: Age (years): 32 (18-55) Weight (kg): 64 (46-86) Hb (g/dL): 14.3 (11.8-15.8) Reticulocyte count (%): 2.4 (1.0-4.0) Platelet count (x1000 per uL): 285 (190-424) Total WBC count (x1000 per uL): 6.6 (4.8-9.3) Methamoglobin (%): 0.5 (0-1.5) AST (U/L): 23 (15-60) ALT (U/L): 26 (10-85) Creatinine (mg/dL): 0.9 (0.8-1.1) Total bilirubin (mg/dL): 0.6 (0.3-1.3) Haptoglobin (g/L): 1.1 (0.5-1.7)

Participant Flow : Part 1, Ascending dose 24 participants Part 2, Single 45 mg dose 16 participants

Adverse events : Haemolysis due to primaquine resulted in stopping of primaquine. Asymptomatic transaminitis probably related to primaquine. Asymptomatic transaminitis due to hepatitis E. Prolapsed intervertebral disc unrelated to primaquine.

Outcome Measures : All data analysis was done in R version 4.2.2. Haemoglobin was measured using Haemocue (daily, two samples) and using a laboratory processed complete blood count (CBC, every 4-5 days). The daily mean haemoglobin was calculated as the mean of the Haemocue (itself the mean of the two values).

Brief Summary of Results : In Part 1, haemoglobin concentrations fell by a median of 3.7 g/dL (-2.1 to -5.9; relative fall of -26% [range:

-15 to -40%)). Primaquine doses up to 0.87 mg/kg/day were tolerated subsequently without clinically significant further falls in haemoglobin. In Part 2, the median haemoglobin fall was 1.7 g/dL (range -0.9 to -4.1; relative fall of -12% [range: -7 to -30%]). The ascending dose primaquine regimens gave 7 times more drug but resulted in double the haemoglobin fall.

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**Deidentified Individual Participant-level Data Sharing**

Plan to share IPD : Yes

Plan description : Anonymised data from this study may be shared following MORU's data sharing and following review by MORU's Data Access Committee upon reasonable request.

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**Publication from this study**

MEDLINE Identifier : No Data

URL link to full text publication : <https://doi.org/10.1101/2023.02.24.2328639>

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