TCTR ID : TCTR20170830002

OTHER ID :

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

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

Tracking Information

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

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

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

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

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 simualtaneously 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 songle dose challenge study of 45 mg.

URL not available

Health Conditions

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

Eligibility

Inclusion Criteria :	1. Male aged between the age of 18 and 65 years 2. Healthy as judged by the examining physician 3. Hb >= 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 >= 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/1.73m2 (the eGFR for males is calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: 13.1 eGFR = 141 x min(Scr/k, 1)power alpha x max(Scr/k, 1)power -1.209 x 0.993 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) 14. Urine analysis (UA) reveals the chronic renal disease defined as RBC >= 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
Intervantion 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 : Podjanee	Middle Name :	Lastname : Jittmala
	Degree : MD	Phone : 6623548333 Ext. : 2404	Email : podjanee@tropmedres.ac

Section B Facility Information and Contact

1. 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	
Facility Contact	First Name : Sasithon	Middle Name :	Last Name : Pukrittayakamee
	Degree : MD	Phone : 6623548333 Ext. : 2404	Email : yon@tropmedres.ac
Facility Contact Backup	First Name : Podjanee	Middle Name :	Last Name : Jittmala
	Degree : MD	Phone : 6623548333 Ext. : 2404	Email : podjanee@tropmedres.ac
Investigator Name	First Name : Sasithon	Middle Name :	Last Name : Pukrittayakamee
	Degree : MD	Role : Site Sub-Investigator	

2. Site Name : The Shoklo Malaria Research unit, Maesot (SMRU)

	City : Mae Sot	State/Province : Tak	Postal Code : 63110
	Country : Thailand	Recruitment Status : Completed	
Facility Contact	First Name : Cindy	Middle Name :	Last Name : Chu
	Degree : MD	Phone : 6655545021 Ext. : No Data	Email : cindy@tropmedres.ac
Facility Contact Backup	First Name : Germana	Middle Name :	Last Name : Bancone
	Degree :	Phone : 6655545021 Ext. : No Data	Email : Germana@tropmedres.ac
Investigator Name	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.

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.

Publication from this study

MEDLINE Identifier : No Data

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