

TCTR ID : TCTR20170830002**Overall Recruitment Status : Completed (Has Results)****OTHER ID :****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 : tmeectropmed@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 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**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 G6PD
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

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 deficiency
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 haemoglobin 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 Degree : MD	Middle Name : Phone : 6622036333 Ext. : 6373	Last Name : Taylor Email : bob@tropmedres.ac
Central Contact Backup	First Name : Podjanee Degree : MD	Middle Name : Phone : 6623548333 Ext. : 2404	Lastname : Jittmala 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 Country : Thailand		
	Facility Contact	First Name : Sasithon Degree : MD	Middle Name : Phone : 6623548333 Ext. : 2404
	Facility Contact Backup	First Name : Podjanee Degree : MD	Middle Name : Phone : 6623548333 Ext. : 2404
	Investigator Name	First Name : Sasithon Degree : MD	Middle Name : Role : Site Sub-Investigator
2.	Site Name : The Shoklo Malaria Research unit, Maesot (SMRU) City : Mae Sot Country : Thailand		
	Facility Contact	First Name : Cindy Degree : MD	Middle Name : Phone : 6655545021 Ext. : No Data
	Facility Contact Backup	First Name : Germana Degree :	Middle Name : Phone : 6655545021 Ext. : No Data
	Investigator Name	First Name : Cindy Degree : MD	Middle Name : Role : Site Sub-Investigator

Section C : Contact for Public Queries (Responsible Person)

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

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

Date of posting of results summaries : 25 February 2023

Date of first journal publication of results : Not yet published

Baseline Characteristics : Ascending 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>
