**Study Title:** A Revised Tafenoquine Dose to Improve Radical Cure for Vivax Malaria -Tafenoquine Dosing revised

**Short title:** TADORE

**Phase of the trial:** Phase-III

**CTA Number:** ET-CT-0042

**Protocol No.:**

**Version No.:** V2.6 dated December 19, 2024

**National Principal Investigator (NPI):** Tamru Shibiru (Dr)

**Trial Site:** Arba Minch General Hospital

**Sponsor:** Oxford

**Ethics Approval date:** April 22, 2024

**Submission Date to EFDA:** December 25, 2023

**EFDA Status of trial (Approval or Rejection):** Approved **Date:** August 19, 2024

**Study Rationale**

Tafenoquine (TQ), as a single dose regimen, has significant advantages over the longer courses of primaquine (PQ) needed to achieve radical cure of *P. vivax*. The current data available show that the recommended fixed dose of 300mg TQ in adults is too low and compromised by a lack of weight-based dosing. To ensure maximal impact on health outcomes, the recommended dose for TQ must be optimized for clinical practice. Our study will assess the efficacy and safety of a higher weight based TQ dose regimen.

**General objective / Study aims**

**Primary endpoint**

- compared between TQRevised and the PQ7 (non-inferiority)
- compared between TQRevised and TQStandard (superiority)

**Primary Objectives**

**Objective**

- To compare the efficacy of a revised weight-based TQ regimen (TQRevised: target dose 7.5mg/kg) with high dose primaquine (PQ7: 7mg/kg over 7 days)
- To compare the antirelapse efficacy of TQRevised with the fixed-dose TQ regimen (TQStandard: 300mg fixed dose)

**Outcome measures**

The incidence risk (time to first event) of any *P. vivax* parasitaemia during the 4-month follow up period as determined by microscopy.

- compared between TQRevised and the PQ7 (non-inferiority)
- compared between TQRevised and TQStandard (superiority)

**Secondary Objectives and Outcome Measures**

**Objective**

- To compare the tolerability and safety of TQRevised, TQStandard and PQ7
- To understand feasibility and acceptability of a weight-based dosing scheme
- To undertake host and parasite molecular analysis, serological analysis and assess markers of inflammation

**Outcome measures**

- The incidence risk (time to first event) of any P. vivax parasitaemia during the 4-month follow up period as determined by microscopy compared between TQStandard and PQ7
- The incidence risk (time to first event) of symptomatic *P. vivax* parasitaemia during the 4 months follow up period as determined by microscopy
- The incidence risk (time to first event) of any *P. vivax* parasitaemia at 6-month follow up as determined by microscopy
- The incidence risk (time to first event) of symptomatic *P. vivax* parasitaemia at 6-month follow up as determined by microscopy.
- The incidence rate (events per person-time) of any *P. vivax* parasitaemia during the 6 months follow up period as determined by microscopy.
- The incidence rate (events per person-time) of symptomatic *P. vivax* parasitaemia during the 6 months follow up period as determined by microscopy
- The incidence risk of developing severe anaemia (Hb < 5g/dl) or moderate (≥5g/dl and <7g/dl) anaemia within 7 and 14 days of starting treatment and/or requiring blood transfusion within the 6 months follow up period.
- The incidence risk of an acute drop in Hb of >25% to <7g/dl within 7 and 14 days of starting treatment
- The number and proportion of adverse and serious adverse events in each arm within 42 days after start of treatment.

**Study Design**

A parallel group open label, randomised, controlled non-inferiority trial in patients with uncomplicated *P. vivax* malaria.

**Study Population**

Only patients with a G6PD activity ≥70%

**Eligibility Criteria**

**Inclusion Criteria:**

- *P. vivax* peripheral parasitaemia (mono-infection)
- G6PD normal status (G6PD activity ≥70% of the adjusted male median as determined by the Standard G6PD (SD Biosensor, ROK))
- Fever (temperature ≥37.5ºC) or history of fever in the preceding 48 hours
- Age ≥18 years
- Haemoglobin at presentation ≥8g/dl
- Written informed consent.
- Living in the study area and willing to be followed for six months

**Exclusion criteria:**

- Danger signs or symptoms of severe malaria
- Pregnant or lactating females
- Regular use of drugs with haemolytic potential
- Known hypersensitivity to any of the study drugs
- History of any psychiatric disorder.
- History of liver disease.
- Age >65 years

**Study Duration**

3 years

**Investigational Medicinal Product**

Tafenoquine

**Intervention (s)**

**Formulation:** tablet
**Dose:** single weight-based dose of TQ (target dose 7.5mg/kg)
**Route of administration:** PO
**Other interventions:**

- PQ7: high dose PQ (total dose 7 mg/kg) over 7 days
- TQ Standard: single fixed dose of 300mg TQ

**Sample size**

790 participants will be enrolled in the TQ Revised and PQ7 arms and 278 in the TQ Standard arm. The total sample size is therefore 1068 patients. A maximum of 450 patients in Ethiopia.

**Evaluator's Risk/Benefit Assessment:**

Given the serious side effects associated with TQ and PQ, adherence to Good Clinical Practice (GCP) is essential. Considering the epidemiology of malaria in Ethiopia, this trial will provide a critical perspective on future treatment modalities.