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

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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.