**Study Title:** Assessing new paediatric tablets of primaquine as radical cure in Ethiopia.

**Short title:** Assessing Paediatric Primaquine in Ethiopia (DPP-APPE)

**Phase of the trial:** Phase 2

**CTA Number**: ET-CT-0033

**Protocol No.:** NA

**Version No.:** 3.3

**National Principal Investigator (NPI):** Dr. Endalamaw Gadisa

**Trial Site:** Health center at Arbaminch Zuriya woreda (SNNPR)

**Sponsor:** The University of Oxford

**Ethics Approval date:** 12/07/2021

**Submission Date to EFDA:** 08/06/2022

**EFDA Status of trial (Approval or Rejection):** Approved **Date:** 05/06/2024

**Study Rationale**

- Drug formulations that children are able to use and comfortable to take type has been overlooked for many years. The availability of pediatric drugs in the right doses, taste and odour/flavour is critically important. Currently, most of pediatric medicine available on the market are derived from adult dose by crushing or dividing, as a consequence inadequate drugs might be given for the children; this will result in treatment failure or drug resistance. Also, children might be exposed to un necessary drug related side effects
- Measurement of blood or plasma concentration of primaquine (PQ) and its metabolite at different time interval during follow-up of the patient will allow to reliably assess the risk and time of parasite clearance from the blood, which indicates the efficacy of the study drugs. Also, as the drug in the blood is effective to improve the clinical and parasitological outcomes in individuals, which laterally tell us the effectiveness of the drug against the hypnozoite stage in the liver. On the other hand, acceptability of medicine has emerged as a key factor for compliance in paediatric and consequently, for treatment safety and effectiveness.

**General objective / Study aims**

- To assess the acceptability, pharmacokinetics, therapeutic efficacy and safety of new generic PQ regimes as radical cure for uncomplicated vivax malaria among children aged more than 6 months and < 16 years, Ethiopia.

**Primary objective**

**Objective:** Assess the anti-relapse efficacy and safety of daily or weekly primaquine using new generic formulations in children aged 6months to < 16 years

**Outcome measures:** Recurrence of P. vivax parasitaemia over 6 months

**Secondary Objectives and Outcome Measures**

**Objective**

- Determine the haematological response of daily or weekly primaquine using new generic formulations in children aged 6m to < 16 years
- Evaluate the acceptability of new generic PQ regimes in vivax malaria patients 6m to < 16 years
- Characterise PQ and carboxyPQ disposition
- Assess CQ exposure
- Characterise cytochrome P450 2D6 activity
- Characterise host genetics for inherited blood disorders
- Determine Day 28 parasitological and clinical efficacy
- Determine asexual parasite and gametocyte dynamics
- Determine parasite genetics
- Assess the safety of daily or weekly primaquine using new generic formulations in children aged 6m to < 16 years
- Assess socioeconomic factors related to malaria

**Outcome measures**

- Haemoglobin concentrations over time
- Clinsearch acceptability test score (CAST)
- PQ and carboxyPQ concentrations
- Day 7 CQ concentration
- CYP 2D6 polymorphisms
- Presence of sickle cell trait/disease, thalassaemia, and glucose 6-phosphate dehydrogenase (G6PD) variants
- Day 28 rate of adequate clinical and parasitological response (WHO criteria)
- Parasite clearance rate
- Parasite genotype and putative molecular markers of chloroquine resistance
- Adverse events
- proportions of patients/careers responding to specific questions and the mean values of household income

**Study Design**

- This a post registration phase 2b study and involves 3 study designs; field (open label single arm trial), acceptability & qualitative studies.

**Study Population**

- The population of interest consists of patients ≥ 6 months of age and <16 year and living within 20 km radius of the health center and diagnosed by microscopy with uncomplicated *P. vivax* mono-infection or *P. vivax (Pv)* and *P. falciparum* (Pf) mixed infection.

**Eligibility Criteria**

**Inclusion Criteria:**

- Those living within 20 km of the catchment of the health facility with a traceable address or phone contact number
- Parent/legal guardian is willing to comply with the study protocol and visit schedule, including attendance in person for all necessary visits at study site
- Able to give assent for patients aged 12 – 15 years
- Parental/legal guardian informed written consent
- Age ≥ 6 months and < 16 years at the time of consent
- Weight ≥ 5.0 kg
- Slide-confirmed *P. vivax* mono- or mixed infections
- Axillary temperature ≥ 37.5º C or history of fever during the previous 10 days
- Ability to swallow oral medication

**Exclusion criteria:**

- General danger signs or symptoms of severe malaria (see Annex 3)
- Haemoglobin (Hb) < 5 g/dL
- Presence of febrile conditions caused by diseases other than malaria (e.g. measles, acute lower respiratory tract infection, COVID-19, severe diarrhoea with dehydration)
- COVID-19 positive by a lateral flow antigen test
- Serious or chronic medical condition (e.g. cardiac, renal, hepatic diseases, sickle cell disease)

- History of hypersensitivity to study or rescue medication in this study
- Taking regular medication which may interfere with antimalarial PK or efficacy (see Annex 4)
- Severe malnutrition in a child aged between 6-59 months as defined by presence of symmetrical oedema involving at least the feet or a mid-upper arm circumference < 115 mm
- Known pregnancy or urinary pregnancy test (UPT) positive at screening visit

**Study Duration**

- 18 months

**Investigational Medicinal Product**

- Primaquine tablet

**Intervention (s)**

Formulation: Primaquine (2.5, 3.75, 7.5 & 15 mg PQ base)

Dose: 0.25 mg/kg for daily primaquine and 0.5 mg/kg for the weekly regimen

Route of administration: Oral

**Sample size**

- 120 children between 6 months and <16 years and about 25 mothers/legal guardians for focus group discussions (FGD).

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

- The intervention could lead to a better management of the disease with improved adherence with a reduced risk of adverse effect. Hence, the current trial is approved, with due consideration given to the safety of the participants, and the trial will follow the principles of Good Clinical Practice.