Safety and efficacy of a single low-dose of primaquine for treatment of uncomplicated *Plasmodium falciparum* malaria based on cytochrome P450 (CYP) 2D6 enzyme activity in Bagamoyo district, Tanzania.

Summary

Background: The World Health Organization (WHO) recommends addition of a single low-dose (0.25 mg/kg) of primaquine to standard artemisinin-based combination therapy (ACT) for elimination of *Plasmodium falciparum* malaria in low transmission-settings and for containment in areas threatened by artemisinin resistance. The drug has shown to be safe and efficacious, and can probably be employed in malaria endemic sub-Saharan Africa for control of the infection. However, primaquine is metabolized mainly by an enzyme (cytochrome P450 (CYP) 2D6), which is known to be highly polymorphic. This polymorphism has led to people having either, no, reduced, normal or increased enzyme activity. The polymorphic nature of the enzyme is thought to compromise safety and efficacy of primaquine, particularly in individuals with reduced or no CYP2D6 enzyme activity. This trial, therefore, assessed safety and efficacy of 0.25 mg/kg single-dose of primaquine when added to standard artemether-lumefantrine regimen for clearance and blocking the transmission of *P. falciparum* gametocytes in patients with no/reduced enzyme activity as compared to those with normal/increased enzyme activity in Bagamoyo district, Tanzania.

Methods: Between June 2019 and January 2020 children aged 1-10 years, attending at Yombo dispensary, Bagamoyo district, with confirmed microcopy-determined uncomplicated P. falciparum malaria were enrolled in the study. The enrolled patients were treated with a standard artemether-lumefantrine regimen plus 0.25 mg/kg single-dose primaquine and followed up for 28 days for clinical and laboratory assessment. Primaquine was administered with the first dose of artemether-lumefantrine. Safety assessment involved direct questioning and recording of the nature and incidence of clinical signs and symptoms, and measurement of hemoglobin (Hb) concentration. Blood samples collected from 100 patients were used for assessment of post-treatment infectiousness on day 7 using mosquito membrane feeding assays. Molecular methods were used to determine CYP2D6 and glucose-6-phosphate dehydrogenase (G6PD) status. The primary outcome was the safety of 0.25 mg/kg single-dose primaquine based on CYP2D6 status.

Results: In total, 157 children (median age 6.4 (Interquartile range 4.0-8.2) years) were recruited, of whom 21.0% (33/157) and 12.7% (20/157) had reduced CYP2D6 and deficient G6PD activity, respectively. Day 3 mean absolute Hb concentration reduction was 1.50 g/dL (95% confidence

interval [CI]: 1.10-1.90) and 1.51 g/dL (95%CI:1.31-1.71) in reduced and normal CYP2D6 patients, respectively (t=0.012, p=0.990). The day 3 mean absolute Hb concentration reduction in G6PD deficient, G6PD normal and heterozygous female was 1.82 g/dL (95%CI: 1.32-2.32), 1.48 g/dL (95%CI: 1.30-1.67) and 1.47 g/dL (95%CI: 0.76-2.18), respectively (F=0.838, p=0.435). Sixteen percent (16/98) of the patients each infected at least one mosquito on day 7, and of these, 10.0% (2/20) and 17.9% (14/78) had reduced and normal CYP2D6 enzyme activity, respectively (x^2= 0.736, p=0.513).

Conclusion: Single-dose 0.25 mg/kg primaquine was safe and sufficient for reducing transmission of *P. falciparum* gametocytes regardless of CYP2D6 or G6PD status.