Background In Zambia, malaria is one of the leading causes of morbidity and mortality, especially among under five children and pregnant women. For the latter, WHO recommends the use of Artemisinin-based Combinations Treatments (ACTs) in the
second and third trimester of pregnancy. In a context of limited information on ACTs, the safety and efficacy of three ACTs, namely artemether-lumefantrine (AL), mefloquine-artesunate (MQAS) and dihydroartemisinin-piperaquine (DHAPQ) were assessed in malaria-infected pregnant women.

**Methods** Trial was carried out between July 2010 and August 2013 in Nchelenge district, Luapula Province, an area of high transmission, as part of multi-centre trial. Women in second or third trimester of pregnancy and with malaria were recruited and randomized to one of three study arms. Women were actively followed up for 63 days, and then at delivery and one year post-delivery.

**Results** Nine hundred pregnant women were included, 300 per arm. PCR-adjusted treatment failure was 4.7% (12/258) (95% CI:2.7–8.0) for AL, 1.3% (3/235) (95%CI:0.4–3.7) for MQAS and 0.8% (2/236) (95%CI:0.2–3.0) for DHAPQ, with significant risk difference between AL and DHAPQ (p=0.01) and between AL and MQAS (p=0.03) treatments. New infections during follow up were more frequent in AL (Hazard Ratio (HR):4.70; 95%CI:3.18–6.94; p<0.01) and MQAS (HR:1.59; 95%CI:1.02–2.46; p=0.04) arms compared to DHAPQ arm. PCR-adjusted treatment failure was significantly associated with women under 20 years [HR5.35 (95%CI:1.07–26.73; p=0.04)] and higher malaria parasite density [3.23 (95%CI:1.03–10.10; p=0.04)], and still women under 20 years [1.78, (95%CI:1.26–2.52; p<0.01)] had a significantly higher risk of new infections. Unadjusted for treatment, low treatment dosage per kg body weight was significantly associated with the risk of new infections (HR:1.72; 95%CI:1.29–2.28; p<0.01). The three treatments were generally well tolerated. Dizziness, nausea, vomiting, headache and asthenia as Adverse Events (AEs) were more common in MQAS than in AL or DHAPQ (p<0.001). Birth outcomes were not significantly different between treatment arms.