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**Title:** Pharmacokinetics, Clinical and Safety Outcomes of Pyronaridine/artesunate Treatment of Acute *Plasmodium falciparum* Malaria in Uganda

**Author Block:** Patrice Piola<sup>1</sup>, Lawrence Fleckenstein<sup>2</sup>

<sup>1</sup>MSF Epicentre, Mbarara, Uganda, <sup>2</sup>The University of Iowa, Iowa City, IA, United States

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Pyronaridine/artesunate (Pyramax<sup>®</sup>) is a novel treatment of *Plasmodium falciparum* malaria. A randomised, multicentre, Phase II, dose-ranging clinical study was conducted to assess the safety and efficacy of fixed dose, orally administered pyronaridine and artesunate in adult patients with acute uncomplicated *Plasmodium falciparum* malaria. Pyronaridine pharmacokinetics was studied in a sub-population of 16 Uganda patients. Treatment with pyronaridine/artesunate: 6+2 mg/kg (n=5), 9+3 mg/kg (n=5), 12+4 mg/kg (n=6), was once daily for 3 days being closely matched for demographic characteristics. Pyronaridine/artesunate treatment resulted in cure at Day 28 for all patients treated with each of the dose groups and this effect continued out to Day 42. All patients were clear of parasites by Day 2. The concentration pyronaridine in whole blood was measured using a previously validated LC-MS method. Noncompartmental pharmacokinetic analysis yielded mean ( $\pm$ SD) values for  $C_{max}$  of  $91.9 \pm 30.8$ ,  $156.8 \pm 57.1$  and  $226.1 \pm 157.5$  ng/mL following 6, 9, 12 mg/kg body weight oral doses, respectively. The corresponding values for  $AUC_{(0-\infty)}$ ,  $T_{1/2}$ , and  $T_{max}$  were  $749 \pm 603$ ,  $1036 \pm 286$ ,  $1134 \pm 624$  ng/mL\*d,  $19.1 \pm 5.9$ ,  $15.9 \pm 5.0$ ,  $14.6 \pm 6.6$  d, and  $5.3 \pm 2.0$ ,  $6.2 \pm 6.3$ ,  $7.6 \pm 4.9$  h, respectively. The pyronaridine blood level profile shows a very pronounced distribution and elimination phase. A prominent second peak was noted in the pyronaridine blood level profiles for some patients. The elimination half-life is longer than previously reported, resulting from a more sensitive pyronaridine assay methodology and prolonged blood sampling. The pyronaridine  $C_{max}$  (following the third dose) was lower in malaria patients compared with healthy volunteers, suggesting that malaria patients have a larger pyronaridine volume of distribution. Pyronaridine/artesunate treatment was well tolerated in this study.

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111 Deer Lake Road, Suite 100

Deerfield, IL 60015 USA

[info@astmh.org](mailto:info@astmh.org)

All questions can be directed to ASTMH headquarters at [info@astmh.org](mailto:info@astmh.org)