randomization code will be broken in August 1997 and the results of the field trial will be presented and discussed at the meeting.

9 *IN VITRO* ACTIVITY OF PYRONARIDINE AGAINST 161 AFRICAN ISOLATES (SENEGAL) OF *PLASMODIUM FALCIPARUM*. Pradines B*, Tall A, Parzy D, Spiegel A, Fusai T, Hienne R, Trape JF, and Doury JC. Unite de Parasitologie, Institut de Medecine Tropicale du Service de Sante des Armees, Marseille, France; Service d'Epidemiologie, Institut Pasteur, Dakar, Senegal; and Laboratoire de Paludologie, ORSTOM, Dakar, Senegal.

The *in vitro* activities of pyronaridine, and of chloroquine, quinine, cycloguanil, pyrimethamine, amodiaquine, and artemether were evaluated against 161 isolates of *Plasmodium falciparum* from Senegal (Dielmo, Ndiop, Pikine), using an isotopic, micro, drug susceptibility test. The mean IC_{50} values (50% inhibitory concentration) of the 161 isolates from Senegal to pyronaridine was 3.77 nM (CI 95% 3.10 - 4.44). Pyronaridine was more potent than chloroquine against susceptible parasites (2.8 nM versus 35.7 nM). It was signifificantly less potent ($p < 0.002$) against chloroquine-resistant isolates (IC_{50} = 4.6 nM) when compared with chloroquine-susceptible isolates (IC_{50} = 2.8 nM). Based on statistical calculation using the present data (mean IC_{50} + 2 standart deviations), the cutoff value for *in vitro* susceptibility decrease to pyronaridine is IC_{50} greater than 15 nM. 8 isolates (5%) showed $IC_{50} > 15$ nM. A significant positive correlation, suggesting *in vitro* cross-resistance among these drugs was found between pyronaridine and artemether ($r^2 = 0.45$, $p < 0.001$), pyronaridine and quinine ($r^2 = 0.44$, $p < 0.001$), pyronaridine and amodiaquine ($r^2 = 0.34$, $p < 0.001$), and pyronaridine and chloroquine ($r^2 = 0.19$, $p < 0.001$). The present *in vitro* findings require comparison to clinical studies.

10 COMPARATIVE SINGLE-DOSE PHARMACOKINETICS OF PYRONARIDINE SOLUTION AND A NEW CAPSULE FORMULATION IN HEALTHY NORMAL VOLUNTEERS. Navaratnam V, Looareesuwan S, Ismail S, Jamyaraman SD, Chinwongprom K, Mansor SM, Srivilir it S, Wernsdorfer WH, and Olliaro P*. Centre for Drug Research, Universiti Sains Malysia, Penang, Malaysia; Bangkok Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand; University of Vienna, Austria; and UNDP/ WorldBank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), Geneva, Switzerland.

Chinese pyronaridine formulated as enteric-coated tablets is reportedly effective in uncomplicated falciparum malaria, including two recent studies in Cameroon and Thailand. However, two major problems need to be addressed in trying to develop a rational dosing regimen: the scarcity of basic pharmacokinetic data and the poor bioavailability of the existing Chinese product -contributing to the high treatment costs (US$ 3-4/ treatment). This has prompted WHO/TDR to initiate a development program aiming at a better and lower cost drug to meet international standards for registration. Under this programme new capsules dosed 50 and 100 mg have been formulated in Malaysia under GLP conditions using Chinese raw material independently analysed. The new capsules had dissolution profiles of 98-101% and rapid release (>95% within 2 minutes - standard dissolution test USP). In addition, also the development of a suitable analytical methods for pyronaridine in body fluids presented various difficulties. This randomised, cross-over Phase I study was undertaken to establish dose pharmacokinetics of pyronaridine tetraphosphate at 6mg/kg in aqueous solution vs gelatine capsules (with a 19 day wash-out) using a novel HPLC-F validated assay. In most patients drug was detectable within 30' from intake. The two formulations did not differ significantly although tmax was shorter and Cmax was higher with solution (6.3±7.3 vs 11.9±13.3 h; 154±86 vs 120±41 ng/ml respectively). The mean t1/2 was160±59 and 191±13.3 h, respectively. Individual concentration-time profiles fluctuated as from 24 h after drug intake; relatively high concentrations were maintained at almost even level for over 6 days but individual levels may drop below IC90 with time. No significant toxicity was apparent. Clinical laboratory values fluctuated over time around the baseline values. Pyronaridine appears to be well tolerated after single administration of either solution or capsules at 6mg/kg. Multiple dose regimen or combination chemotherapy is required. The pharmacokinetics profiles generated by this study were distinctly different from what was expected based on previously reported Chinese data with EC tablets (eg, t1/2 was almost 3 times longer). These observed differences are primarily attributable to the different formulations used in this study.

11 STEREOSELECTIVE INTERACTION OF HALOFANTRINE WITH HUMAN CYTOCHROME P-450 ISOFORMS *IN VITRO*. Flockhart DA, Karle JM, and Wesche D*. Division of Clinical Pharmacology, Georgetown University Medical Center, Washington, DC; and Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC.

Halofantrine is a phenanthrenemethanol antimalarial which is known to be metabolized to *N*-desbutylhalofantrine. Recent studies demonstrated that halofantrine in the isolated perfused heart prolonged QT

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Disney's Coronado Springs Resort
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