

Pyronaridine Artesunate Combination: Phase I Clinical and Pharmacokinetic Study Results

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Pyronaridine Artesunate FCT

Advantages versus other antimalarials

- Rapid onset of action artesunate plus intermediate half-life of pyronaridine supports once a day regimen for three days
- Pyronaridine not available as monotherapy and not extensively deployed
- Novel formulation with improved bioavailability and stability
- Affordable and competitive price to both public and private sector

Pyronaridine Artesunate FCT

Phase I Programme Overview

- Double-blind, Randomized, Placebo-controlled, Four Part Study
- Single- and multiple-dose finding plus food effect and drug interaction
- Ascending doses (PP:AS) from 6:2mg/kg to 15:5 mg/kg
- Male and female healthy volunteers (19 to 40 years) conducted at Phase I Unit of SNU, Korea

Phase I Safety Evaluations

- Single and Multiple ascending dose:
 - Adverse Events
 - 12-lead resting ECGs
 - Haematology, blood chemistry, urinalysis
 - Physical examinations, vital signs
- Safety data were reviewed prior to each dose escalation

Results

Phase I Safety Evaluation Results

- Single and Multiple ascending dose:
 - No clinically significant changes in 12-lead resting ECGs
 - No clinically significant changes in haematology, blood chemistry, urinalysis
 - No changes in physical examinations, vital signs

Phase I

Demographics: multiple ascending dose

	Dose PA:AS (mg/kg)				
	6:2 N = 6	9:3 N = 6	12:4 N = 6	15:5 N = 6	Placebo N = 8
Age (years) (SD)	24.2 (3.5)	23.0 (2.0)	22.2 (1.3)	23.2 (0.8)	24.0 (3.9)
Gender M/F	4/2	4/2	3/3	4/2	4/4
Weight (kg) (SD)	63.5 (6.0)	60.0 (5.9)	59.6 (8.0)	60.8 (7.4)	60.2 (6.2)
BMI (SD)	22.8 (0.9)	21.5 (1.1)	21.5 (0.8)	20.9 (0.4)	21.2 (1.4)

Phase I

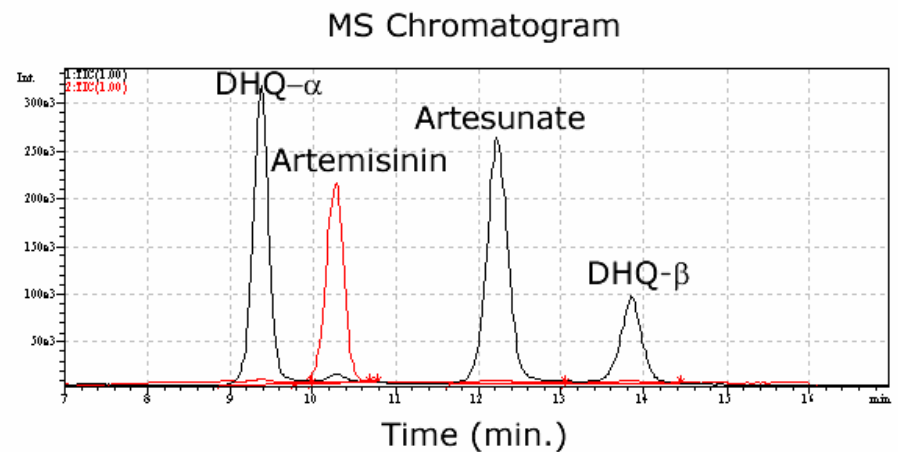
Multiple ascending dose AEs: body system

	Dose PA/AS (mg/kg)				
Body System (No. Subjects)	6:2 N = 7	9:3 N = 7	12:4 N = 7	15:5 N = 7	Placebo N = 8
Total	2	4	5	6	3
Gastrointestinal	1	3	4*	6*	1
General and administration site	0	0	1	1	0
Hepatobiliary	0	0	0	1	0
Infections	0	0	0	0	1
Musculoskeletal and connective tissue	1	0	0	1	1
Nervous system	1	0	2	0	2
Respiratory, thoracic and mediastinal	1	1	0	1	1
Skin and subcutaneous	0	0	1	1	0

*Principally nausea and diarrhoea

LC/MS Assay for Artesunate & Dihydroartemisinin (DHA)

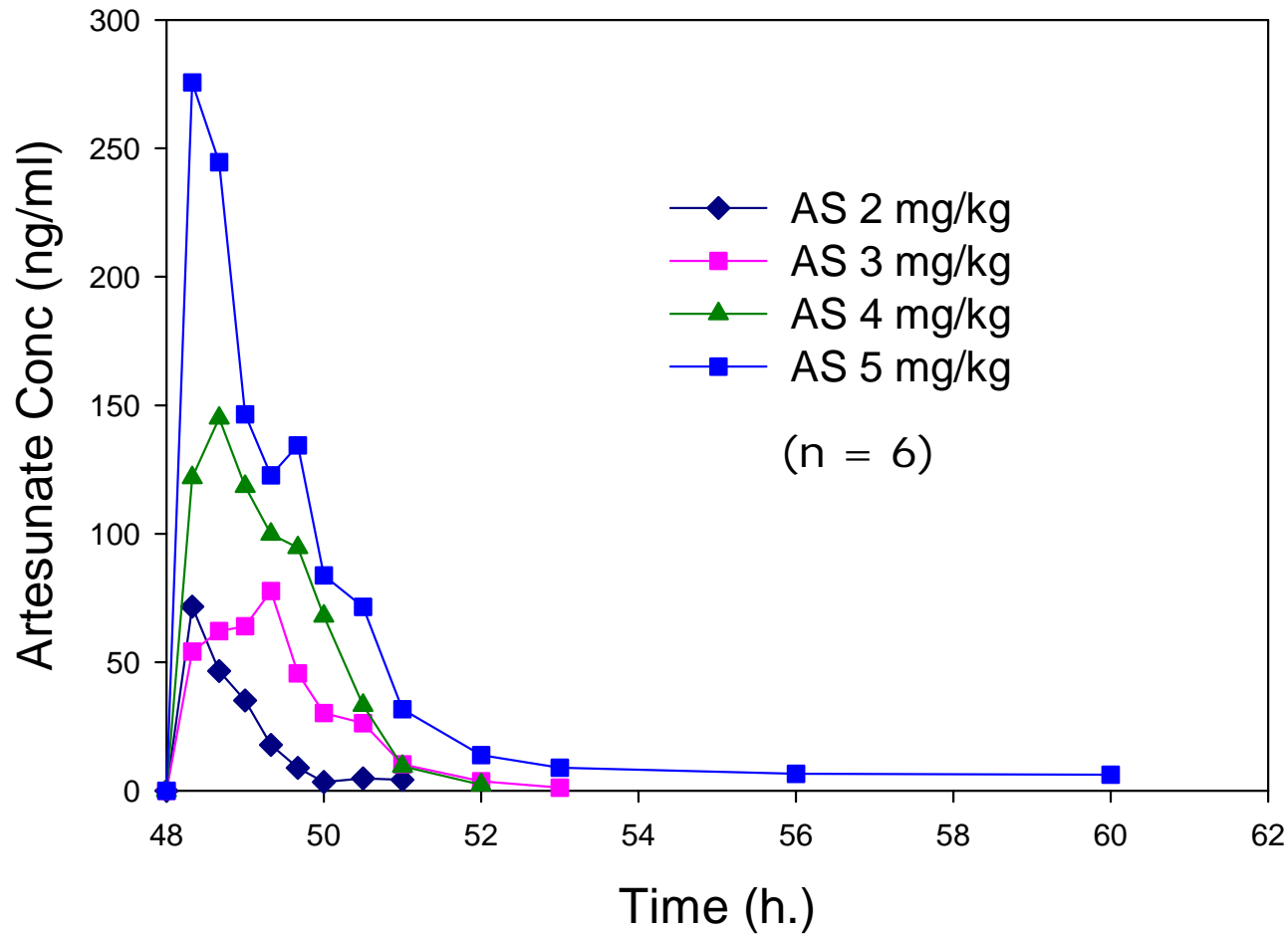
- Requires 0.5 ml plasma
- Artemisinin Int. Std.
- Run time 15 min.
- SPE Extraction
- Recovery ~ 90%
- Sensitivity = 1 ng/ml



Naik, H. et al., J. Chromato., Biomed. Appl.,
816:233-242, 2005.

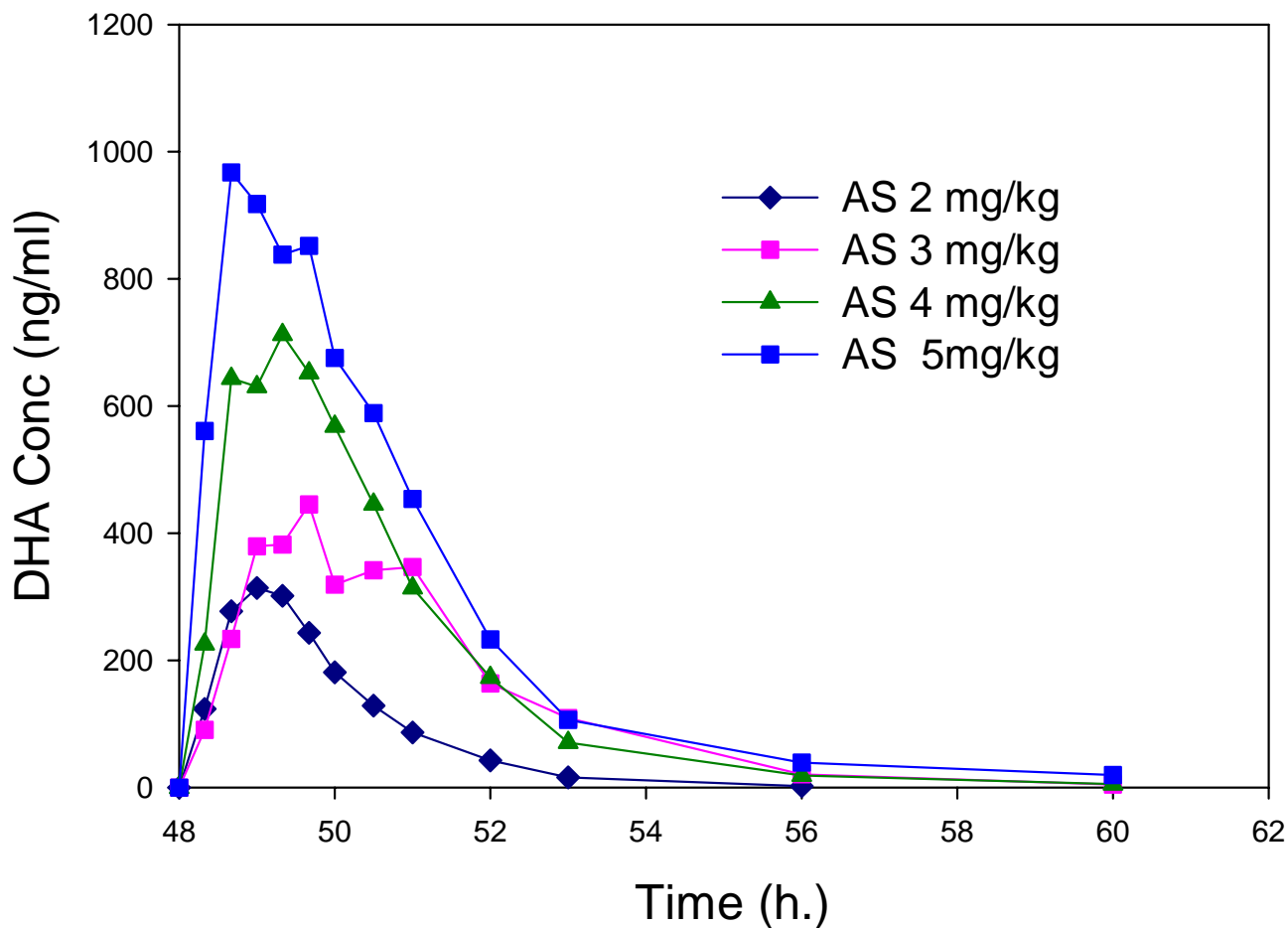
Phase I Multiple Dose Study

Artesunate Profiles



Phase I Multiple Dose Study

Dihydroartemisinin Profiles



Phase I Multiple Dose

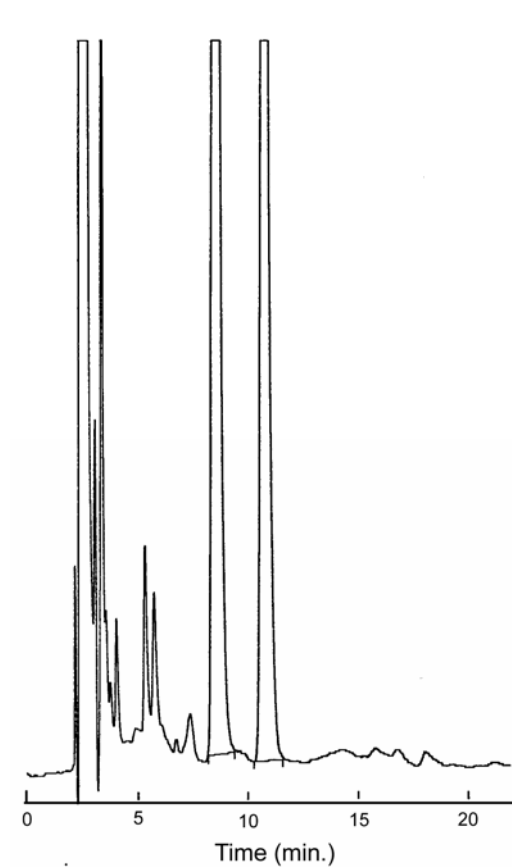
DHA PK parameters

Dose (mg/kg)	Tmax (h.)	Cmax (ng/ml)	AUC (ng/ml*h)	T _{1/2} (h.)
2	1.3 ±0.7	366 ±165	708 ±284	1.0 0.3
3	2.3 ±0.9	528 ±156	1550 ±735	1.9 1.8
4	1.5 ±0.7	845 ±459	2055 ±983	2.0 0.3
5	1.0 ±0.5	1095 ±404	2982 ±711	1.3 0.3

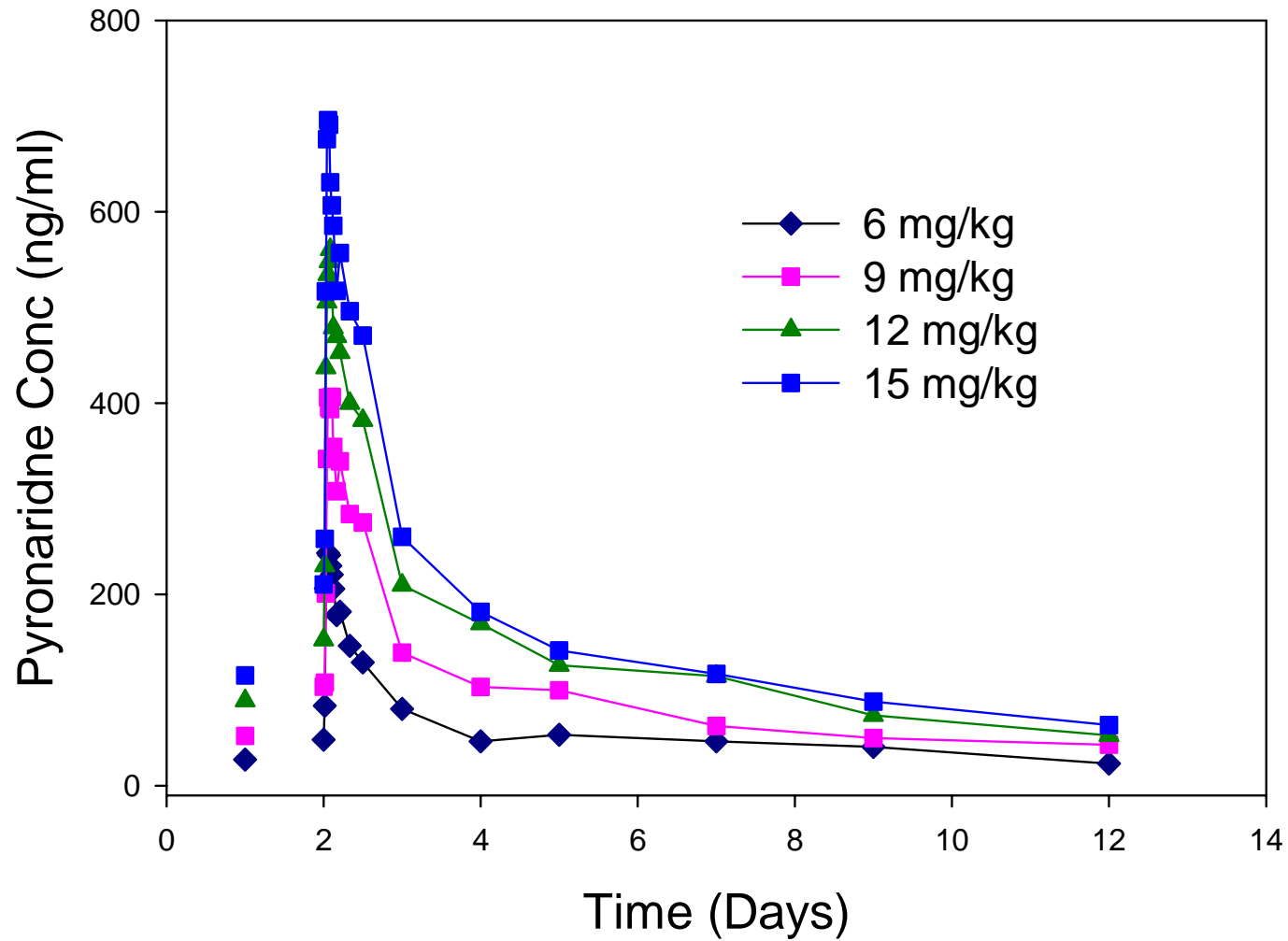
HPLC Assay for Pyronaridine in Blood

- UV detection
- Requires 0.5 ml blood
- Amodiaquine Int. Std.
- Run time 23 min.
- Liquid/liquid Extraction
- Sensitivity = 5.7 ng/ml

Chen and Fleckenstein, J. Chromato.,
Biomed. Appl. 752:39-46, 2001.



Phase I Multiple Dose *Pyronaridine*



Phase I Multiple Dose
Pyronaridine PK Parameters

Dose (mg/kg)	Tmax (h.)	Cmax (ng/ml)	AUC (ng/ml*d)	T _{1/2} (d.)
6	2.1 ±0.02	171 ±32.9	264 ±168	9.7 ±8.1
9	2.0 ±1.3	262 ±84.7	288 ±58.3	6.8 ±1.6
12	1.6 ±0.3	467 ±217	523 ±168	6.6 ±1.4
15	4.0 4.3	774 ±285	865 ±199	7.0 ±2.0

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Summary Phase I Safety and Tolerability

- Combination was well tolerated up to PP 15 mg/kg + AS 5 mg/kg
- No SAEs
- Dose limiting AEs were GI effects and were mild in nature
- No other significant dose-dependent abnormalities in laboratory tests, physical examinations and ECG findings
- PK supports once a day regimen

Pyronaridine Artesunate FCT

- Novel GMP formulation with improved bioavailability and stability
 - Impact on cost of goods
 - Impact on shelf life (target three years)
- GLP Non-clinical studies per ICH guidelines
- Phase I programme completed
- Phase II- Dose Finding:
 - 50% completed



Pyronaridine Artesunate FCT MIM Malaria Conference 2005

Curing Malaria Together



Medicines for Malaria Venture

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