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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00386503
		Study Code:	ARAMF_L_01570
Generic drug name:	COARSUCAM™	**Date:**	03/Aug /2007

Title of the study: A randomized, open-label, cross-over study, to compare the bioavailability of the fixed combination of amodiaquine and artesunate (COARSUCAM™) after single oral administration under fed and fasted conditions in healthy subjects (Study number: ARAMF_L_01570)

Investigator(s): Anne KERVELLA, MD and Eric LESAUVAGE, MD, MEDISCIS, Z.A. des Greffières, Rue Auguste Perret, 17140 LAGORD, France

Study center(s): One study center in France

Publications (reference): Not applicable

Study period:

Date first subject enrolled: 05/Jun/2006

Date last subject completed: 22/Dec/2006

Phase of development: Exploratory

Objectives: The objectives of the study were to evaluate the interaction with food after a single oral dose of a fixed combination of amodiaquine (AQ) and artesunate (AS) (COARSUCAM™) in healthy male subjects as primary objectives and to assess the clinical and biological safety and tolerability of each mode of administration as secondary objectives.

Methodology: A randomized, open-label, cross-over study

Number of subjects: Planned: 22

Randomized: 22

Treated: 22

Evaluated:

Safety: 22

Pharmacokinetics: 22

Diagnosis and criteria for inclusion: Healthy male subjects, aged from 18 to 50 years, weight at screening between 50 and 90 kg, body mass index between 18 and 28 kg/m²

Investigational product: Coarsucam™, fixed combination of 50 mg ARTESUNATE / 135 mg AMODIAQUINE in the same tablet.

Dose: Four tablets corresponding to 200 mg ARTESUNATE and 540 mg AMODIAQUINE

Administration: Oral route

Duration of treatment: Two 10-day investigation periods (separated by a washout period of 6 months), one administration per period on Day 1

Duration of observation:
Screening phase: within 2 to 21 days before the first drug administration.
Evaluation phase: Two 10-day (+/- 1 day) investigation periods. Each administration was separated by a wash-out period of at least 6 months.
Post study visit: during the last visit of Period 2, i.e. 10 days (+/- 1 day) after the last drug administration.

Reference therapy: Not applicable

Criteria for evaluation:

Safety: Safety was evaluated using monitoring of adverse events (AEs), laboratory assessments (hematology, biochemistry and urinalysis), vital signs, electrocardiogram (ECG) parameters, and physical examinations.

Pharmacokinetics: Time course of the plasma concentrations of artesunate, amodiaquine and their pharmacologically active metabolites: dihydroartemisinin (DHA) and desethylamodiaquine (DSA) were used to determine the following parameters when possible:

- For AS, DHA and AQ: T_{max}, C_{max}, $t_{1/2}$, AUC_{0-t} and AUC_{0-Inf}
- For DSAQ: T_{max}, C_{max}, AUC_{0-t}

Pharmacokinetic sampling times and bioanalytical methods:

Sampling:

Amodiaquine and desethylamodiaquine: Blood samples for PK assessments were to be collected on Day 1 of each period at the predose time point and at 0.16; 0.33; 0.5; 0.75; 1; 1.33; 1.66; 2; 3; 4; 6; 8; 12 after dosing and on Days 2; 3; 4; 5;7 and 10.

Artesunate and dihydroartemisinin: Blood samples for PK assessments were to be collected on Day 1 of each period at the predose time point and at 0.16; 0.33; 0.5; 0.75; 1; 1.33; 1.66; 2; 2.5; 3; 4; 5; 6; 8; 10; 12 after dosing and on Day 2.

Assay:

The assays of amodiaquine, artesunate and their respective metabolites, desethylamodiaquine and dihydroartemisinin were performed using a LC-MS/MS method with a lower limit of quantification equal to 1 ng/mL.

Statistical methods:
Pharmacokinetics: Pharmacokinetic parameters of artesunate, dihydroartesiminin, amodiaquine, and desethylamodiaquine were summarized by number of observations, arithmetic and geometric means, SD, coefficient of variation (CV %), standard error of the mean (SEM), median, minimum, and maximum, for each administration condition.
Prior to analyses described below, C_{max}, AUC_{0-t} and AUC_{0-Inf} values were log-transformed.
The food effect was assessed using an analysis of variance with factors Sequence + Subject (Sequence) + Period + Food + Error.
For C_{max}, AUC_{0-t}, and AUC_{0-Inf}, 90% confidence intervals for the ratios of means (fed/fasted) were obtained.
Equivalence was concluded if the 90% confidence intervals for the ratios were entirely within the 0.80 to 1.25 equivalence specifications.
The T_{max} values were compared between administration conditions with a non-parametric median test.

Pharmacodynamics: Not applicable

Pharmacokinetic/pharmacodynamic relationship: Not applicable.

Safety: The safety evaluation was based upon review of descriptive statistics (summary and tables) and individual values [potentially clinically significant abnormalities (PCSAs)]. All AEs, non-treatment emergent adverse events (NTEAEs) and treatment emergent adverse events (TEAEs) coded using the Medical Dictionary for Regulatory Activities (MedDRA) were listed.
Treatment emergent adverse events were summarized (counts and percents) by administration condition.

Summary:

Pharmacokinetic results:

Pharmacokinetic parameters and statistical results for amodiaquine and desethylamodiaquine are summarized in the table below.

Parameters	Treatment Condition	Amodiaquine	Desethylamodiaquine	Amodiaquine ANOVA 90%CI point estimate	Desethylamodiaquine ANOVA 90%CI point estimate
Tmax (h)	Fasting	0.75 (0.33, 3.00)	1.67 (0.75, 8.00)	S	S
	Fed	1.00 (0.55, 1.68)	4.00 (1.33, 6.00)		
Cmax (ng/mL)	Fasting	14.24 ± 4.26 (29.89) [13.61]	141.21 ± 53.19 (37.67) [129.98]	0.01895 (S) [1.066 - 1.3911] 1.218	0.03329 (S) [1.0474 – 1.3921] 1.207
	Fed	17.53 ± 6.07 (34.63) [16.58]	166.92 ± 63.89 (38.27) [156.95]		
AUC_{0-t} (ng.h/mL)	Fasting	74.43 ± 28.00 (37.61) [68.74]	4824.05 ± 1450.48 (30.07) [4612.76]	<0.001 (S) [1.3895 - 1.8255] 1.593	0.027 (S) [1.0348 – 1.2368] 1.131
	Fed	117.55 ± 46.09 (39.21) [109.48]	5394.79 ± 1450.47 (26.89) [5218.49]		
AUC_{0-Inf} (ng.h/mL)	Fasting	103.88 ± 39.36 (37.89) [95.35]	6558.05 ± 1654.16 (25.23) [6353.16]	-*	-*
	Fed	162.00 ± 50.32 (31.06) [154.42]	7553.54 ± 1911.12 (25.30) [7345.67]		
$t_{1/2}$ (hours)	Fasting	12.18 ± 3.71 (30.41) [11.51]	126.45 ± 50.03 (39.57) [118.25]	0.1209 (NS) [0.9892 - 1.337] 1.280	-*
	Fed	15.57 ± 5.31 (34.09) [14.73]	115.27 ± 37.89 (32.87) [109.52]		

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max); Source: @@Appendix 14.2.5.4

* No statistical analysis was performed because the number of available data was too small.

Pharmacokinetic parameters and statistical results for artesunate and dihydroartemisinin are summarized in the table below.

Parameters	Treatment	Artesunate	Dihydroartesiminin	Artesunate ANOVA 90%CI point estimate	Dihydroartesiminin ANOVA 90%CI point estimate
Tmax (h)	Fasting	0.33 (0.17, 0.50)	0.75 (0.50, 3.00)	NS	S
	Fed	0.33 (0.17, 2.50)	1.67 (1.00, 5.00)		
Cmax (ng/mL)	Fasting	181.28 ± 110.97 (61.22) [153.12]	483.27 ± 145.74 (30.16) [462.98]	<0.001 (S) [0.2790 - 0.4652] 0.360	<0.001 (S) [0.4347 – 0.6034] 0.512
	Fed	61.70 ± 30.21 (48.97) [55.17]	253.53 ± 102.09 (40.27) [237.11]		
AUC_{0-t} (ng.h/mL)	Fasting	100.74 ± 51.11 (50.74) [90.24]	768.67 ± 172.82 (22.48) [750.45]	0.2546 (NS) [0.7421 - 1.0584] 0.886	0.1953 (NS) [0.8416 – 1.0219] 0.927
	Fed	87.23 ± 37.08 (42.51) [79.97]	727.20 ± 215.78 (29.67) [695.94]		
AUC_{0-Inf} (ng.h/mL)	Fasting	109.95 ± 52.47 (47.72) [99.46]	773.72 ± 173.80 (22.46) [755.38]	0.4482 (NS) [0.7651 – 1.1093] 0.844	0.1967 (NS) [0.8421 – 1.0221] 0.928
	Fed	90.28 ± 35.38 (39.19) [83.93]	731.91 ± 216.07 (29.52) [700.78]		
$t_{1/2}$ (hours)	Fasting	0.50 ± 0.27 (54.93) [0.44]	1.63 ± 0.57 (34.80) [1.54]	0.05547 (NS) [1.1117 – 2.3019] 1.727	0.1854 (NS) [0.7125 – 1.0328] 0.890
	Fed	0.87 ± 0.58 (66.40) [0.76]	1.42 ± 0.45 (31.98) [1.37]		

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max); Source: @@Appendix 14.2.5.4

Safety results:

No death and no adverse event (AE) with action taken (treatment stopped) occurred during the study.

One serious AE, non treatment related, occurred during the study, leading to hospitalization, during the wash out period between the COARSUCAM™ Fed conditions and the COARSUCAM™ Fasted conditions.

Twenty four (24) AEs occurred during the study, 14 in COARSUCAM™ Fasted Group and 10 in COARSUCAM™ Fed Group, in 12 subjects.
Twelve (12) AEs were treatment emergent AE (TEAEs) and eleven (12) AEs were non-treatment emergent AEs (NTEAE). All adverse events recovered during the study.
The most frequently affected system organs were nervous system disorders (4 episodes NTEAEs of headache and 5 episodes TEAEs). The TEAEs were of mild or moderate intensity.

Some significant changes from baseline were observed for the laboratory parameters, vitals signs, electrocardiograms and weight.
No clinically relevant changes from baseline in mean values of QTc were apparent at any points under fasted and fed conditions.

Date of report: Final version – 03 July 2007