Safety, efficacy, tolerability and first population pharmacokinetic study on fixed-dose artesunate/amodiaquine combination versus combined loose drugs for uncomplicated malaria in Kenyan adults

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DNDi
Drugs for Neglected Diseases *initiative*

Background

- ASAQ is a new and convenient fixed-dose combination (FDC) of artesunate and amodiaquine developed by DND*i* in partnership with Sanofi-Aventis
- Studies on ASAQ have been performed and are ongoing in different countries and patients
- A large study in children in Burkina-Faso compared the FDC with the combined loose drugs to establish the value of the new combination
- In this study, the FDC is compared to the co-packaged in a group of Kenyan adults

Study objectives

- To determine the pharmacokinetic (PK) parameters of the co-formulated FDC AS/AQ and co-packaged in adults with acute uncomplicated *P. falciparum* malaria
- Evaluate the incidence of adverse events
- Determine rates by proportions and cumulative probabilities of patients achieving sustained parasite clearance at D28;

  Parasite reduction ratio at 48h of treatment;

  Parasite and fever clearance rates on D1, D2 and D3
- Compare the proportions of patients with gametocyte carriage during follow up

Study design

- Phase II open-label randomized clinical trial in Chulaimbo Sub District hospital in Kisumu Kenya

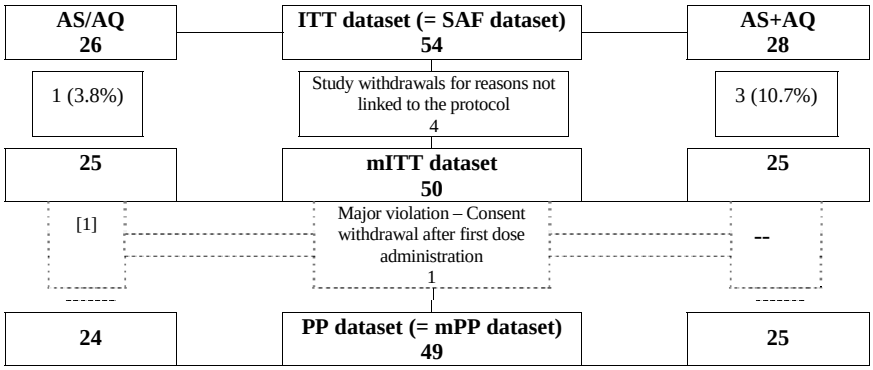
  AS/AQ group (n=26):

AS 200 mg/day and AQ 540 mg/day for three days, 24-h interval

  AS+AQ (FDC) group (n=28):

AS 200 mg/day and AQ 612 mg/day for three days, 24-h interval

Trial profile



ITT population included all randomised patients who received at least one dose of study medication. Patients were analysed according to the treatment they were administered.

mITT population included all randomised patients who received at least one dose of study medication, except for patients withdrawn for reasons not linked to the protocol

Eligibility criteria

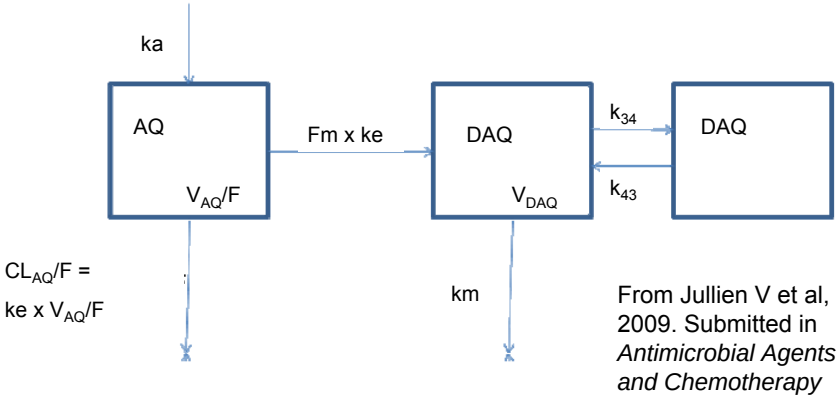
R1

- Age between 18 years and 60 years
- Uncomplicated *P. falciparum* malaria
- Positive *P. falciparum* parasitaemia >1000 asexual parasites/µL
- Either a history of fever in the last 24 h or with a measured fever ≥37.5°C
- Written informed consent

Baseline characteristics (mITT dataset)

Demographics, n (SD)	AS/AQ (n=25)	AS+AQ (n=25)
Age (years)	28.24 (11.49)	27.56 (11.04)
Male, N (%)	11 (44%)	12 (48%)
Weight (kg)	59.96 (9.86)	58.84 (9.11)
Haematology, n (SD)		
WCC (x10^3/µL)	5.59 (1.15)	5.12 (1.62)
Neutrophils (x10^3/µL)	3.37 (1.16)	2.79 (1.56)
Haemoglobin (g/dL)	13.04 (1.89)	13.76 (2.09)
Erythrocytes (x10^6/µL)	4.79 (0.74)	4.96 (0.64)
Biochemistry, n (SD)		
AST (U/L)	32.88 (14.81)	32.67 (12.56)
ALT (U/L)	29.58 (25.16)	30.04 (19.34)

Pharmacokinetic model



From Jullien V et al, 2009. Submitted in *Antimicrobial Agents and Chemotherapy*

1-compartment model with first-order absorption and elimination, and first-order and irreversible transformation into desethylamodiaquine (the active metabolite)

Comparison of data on population PK estimates for AQ and DAQ

Reference	$T_{1/2AQ}$ (h)	CL/F_{AQ} (L/h)	$T_{1/2\alpha DAQ}$	$T_{1/2\beta DAQ}$ (h)
Present results	7.9	3410	0.79	211
Navaratnam, 2009 (11)	2.3 ± 1.4	2504 ± 2000*	NA	201±119
Orrell, 2008 (15)	3.9 ± 1.2	5160 ± 1560	NA	136.9 ± 83.8
Winstanley, 1990 (22)	3.7 ± 1.3	NA	NA	60
Winstanley 1987, (21)	5.2 ± 1.7	6060 ± 1212*	NA	NA

$T_{1/2AQ}$: elimination half-life of amodiaquine, CL/F_{AQ} apparent clearance of amodiaquine, $T_{1/2\alpha DAQ}$: distribution half-life of desethy-amodiaquine, $T_{1/2\beta DAQ}$: terminal half-life of desethyl-amodiaquine, *values derived from reported doses and AUCs

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PK data based on population analysis: some preliminary conclusions

- Mean elimination half-life of DAQ in adult patients was 211 h (8.8 days), which is in line with half-life in children (7.3 to 11.6 days; *Stepniewska K et al, Malaria J, 2009*)
- The new dosage form (FDC) had no effect on the PK parameters of AQ and DAQ
- Differences in bodyweight explain the interindividual variability of the apparent volume of distribution of AQ and the elimination rate constant of DAQ

Efficacy (mITT dataset)

Parasitological cure n (%)/Yes	AS/AQ (n=25)	AS+AQ (n=25)
Not PCR corrected at D28	24 (96.0%)	23 (92.0%)
PCR corrected at D28	24 (96.0%)	25 (100.0%)
Proportion of patients with parasitaemia at D1	8 (33.3%)	9 (36.0%)
Proportion of patients with parasitaemia at D2	0 (0.0%)	2 (8.0%)
Proportion of patients with parasitaemia at D3	0 (0.0%)	0 (0.0%)

- No patients had gametocytes at any visit from D2 to D28, except for one patient (in the AS/AQ group) on D14

Safety (ITT dataset)

	TEAEs, n (%)		Possibly or probably related TEAEs	
	AS/AQ (n=26)	AS+AQ (n=28)	AS/AQ (n=26)	AS+AQ (n=28)
At least 1 solicited TEAE	18 (69%)	19 (68%)	5 (19%)	5 (18%)
At least 1 solicited TEAE of:				
Headache	10 (39%)	12 (43%)	..	..
Weakness	8 (31%)	11 (39%)	..	2 (7%)
Anorexia	7 (27%)	7 (25%)	1 (4%)	..
Nausea	6 (23%)	8 (29%)	..	..
Abdominal pain	6 (23%)	7 (25%)	1 (4%)	1 (4%)
Itching	6 (23%)	3 (11%)	3 (11%)	2 (7%)
Vomiting	4 (15%)	2 (7%)	..	..
Diarrhea	2 (8%)	2 (7%)	..	1 (4%)
Rhinitis	2 (8%)	2 (7%)	1 (4%)	..
Cough	1 (4%)	2 (7%)	..	..

Biochemistry

- ↓ mean bilirubin from D0 to D28
- Slight ↑ in mean ALT between D0 and D7, but by D28 mean ALT had decreased and was slightly lower than at D0
- The values for other biochemical variables remained stable and no clinically significant changes were observed overall

Haematology

- ↓ mean haemoglobin and mean hematocrit in both groups between D0 and D7, but between D7 and D28 values returned towards baseline values
- Mean platelet count increased in both groups between D0 and D7, and then showed a return towards baseline values between D7 and D28
- Mean eosinophil count increased in both treatment groups between D0 and D7. In the AS/AQ group, mean eosinophil count increased further to D28, while in the AS+AQ remained stable
- Two cases of neutropenia; no other significant abnormalities

ECG data analysis

- Changes in mean QT interval during the study were not clinically significant and were related to resolution of disease and disappearance of fever
- AS/AQ FDC does not cause a significant prolongation of the QTc interval when compared to AS+AQ loose treatment
- The effect on heart rate with AS/AQ FDC and AS+AQ were comparable
- There was no significant difference between AS/AQ FDC and AS+AQ on PR and QRS parameters

Conclusions

- AQ and AS in both FDC and co-packaged were highly effective for the treatment of acute uncomplicated *Pf* malaria
- Both combinations were well tolerated
- PK parameters of AQ and DAQ are similar to the previously published, including in children, but elimination half-life of AQ was longer

Acknowledgments

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- Synexel Laboratories for the bioanalytical work
- Dr. Vincent Jullien for the pharmacokinetics

Thank You

Neutrophils over time (ITT dataset)

Neutrophils (10^3/µL) n (SD)	AS/AQ (n=26)	AS+AQ (n=28)
At D0	3.42 (1.17)	2.76 (1.48)
At D7	2.63 (1.15)	2.58 (1.04)
At D28	1.87 (0.91)	2.39 (1.78)