



Phase II, Randomized, Double-Blind Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of Intravenous Artesunate in Children with Severe Malaria

(Clinicaltrials.gov N°: NCT00522132)

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On behalf of the study's SMAC consortium

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Primary and Secondary trial objectives

Primary trial objectives

To evaluate the effectiveness of 2 intravenous GMP artesunate dosing regimens

2.4 mg/kg initially and at 12, 24, 48, and 72 hours

or

4.0 mg/kg initially and at 24 and 48 hours

in clearing *P. falciparum* parasites in children with severe malaria



Primary and Secondary trial objectives

Secondary trial objectives

To Compare

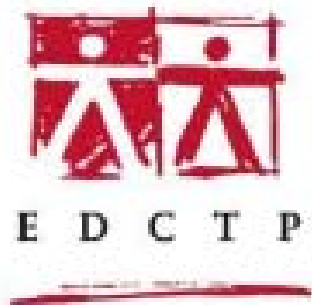
- tolerability
- safety

of the 2 intravenous artesunate dosing regimens.

To evaluation

- pharmacokinetic profile

by patient age and clinical presentation.



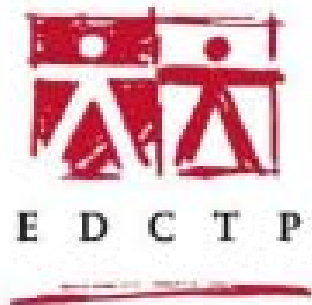
Methods

The study was performed in three clinical centres:

- Albert Schweitzer Hospital, Lambaréné, Gabon
- Université des Sciences de la Santé, Libreville, Gabon
- Queen Elisabeth Central Hospital, Blantyre, Malawi

Study design:

- double-blind, multicenter, randomized, parallel-group study
- Randomization to 1 of 2 cohorts



Methods

Recruitment between October 2007 and June 2008:

- Hospitalization during administration of study drug
- Follow up visits: days 7, 14 and 28

Main objective:

- Evaluation of the efficacy of the 2 dosing regimens



Methods

Primary outcome measure:

- parasite reduction rate at 24h after the start of treatment

Primary endpoint:

- proportion of patients with at least 99% parasite reduction at 24 h after start of therapy



Methods

Secondary objectives:

Comparison of

- Safety, Tolerability, Efficacy
- Incidence of adverse events and significant laboratory changes
- Mortality and neurological sequelae in patients that presented with cerebral malaria



Results

Randomization of 197 patients:

- 50 in Lambaréné,
- 49 in Libreville
- 98 in Blantyre

Safety population: 194 subjects
ITT population: 182 subjects
PP population: 171 subjects

Overall mortality: 1.1% in PP population (2 deaths)

- A 4 year old girl who died 2 days after hospitalization
- A 34 months old boy who died one day after admission



Results

Signs and symptoms and initial parasitaemia in the two groups on the ITT population

	5 dose group	3 dose group
Pulse rate, mean (SD)	149 (26)	144 (24)
Systolic blood pressure, mean (SD)	100 (13)	100 (12)
Diastolic blood pressure, mean (SD)	59 (15)	60 (11)
Respiratory rate, mean (SD)	44 (13)	42 (13)
Body temperature in C, mean (SD)	38.3 (1.1)	37.8 (1.2)
Severe anaemia	17%	15%
Hyperlactataemia	19%	19%



Results

Signs and symptoms and initial parasitaemia in the two groups on the ITT population

	5 dose group	3 dose group
Hyperparasitaemia	40%	40%
Hypoglycaemia	2%	2%
Jaundice	20%	11%
Haemoglobinuria	3%	7%
Respiratory distress	8%	7%
Severe vomiting	18%	23%
Prostration	51%	35%
Initial parasitaemia per microL, median (range)	195,200 (869-1,870,264)	150,500 (1127-1,800,860)



Efficacy

Primary efficacy endpoint: 99% parasite clearance at 24h

	5 dose group	3 dose group
PP	85% (77%-93%)	78% (69%-87%)
ITT	86% (79%-93%)	76% (69%-86%)



Efficacy

100%, 99%, 90% and 50% parasite clearance in the two groups on the ITT population

	5 dose group	3 dose group
PC100 in hours Median (25% and 75% IQ)	36 (30-48)	36 (30-48)
PC99 in hours Median (25% and 75% IQ)	24 (18-24)	18 (18-30)
PC90 in hours Median (25% and 75% IQ)	18 (12-18)	12 (12-18)
PC50 in hours Median (25% and 75% IQ)	12 (6-12)	12 (6-12)



Conclusion

- no significant difference between treatment groups
- simple 24 hourly, 3-dose regimen is as good as 5-dose regimen
- 3-dose regimen should be further studied and developed to licensure for treating severe malaria in children



Consortium

SMAC (investigators)

MMV (sponsor)

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EDCTP (funding body)



MANY THANKS for your attention