A Simplified Artesunate Regimen for Severe Malaria in Children

6th EDCTP Forum, Addis Ababa, Ethiopia
10 October 2011, Peter G. Kremsner
Goal of Project:

Optimization of parenteral Artesunate-treatment of children with severe malaria in Africa with a simplified administration scheme.

Project Design:
Dose Finding Study (Phase II):

Randomized, double-blind, two arm and placebo-controlled trial

- MMV (Sponsor)
- EDCTP (Funding Body)
- WRAIR (Drug Donor)
- ITM, Tübingen & St. George‘s, London (Project Team)

- SMAC (Investigators)
  - Albert Schweitzer Hospital, Lambaréné, Gabon – Saadou Issifou
  - Université de Médecine et Science de la Santé, Libreville, Gabon – Maryvonne Kombila
  - Queen Elizabeth Central Hospital, Blantyre, Malawi – Terrie Taylor
Dose Finding Study – Study Objectives:

Randomization of 197 patients at 3 study sites in Africa

Primary objectives:

Evaluation of the efficacy of two iv artemisinine dosing regimens:

- **Cohort 1**: 5 x 2.4 mg/kg (0, 12, 24, 48, 72 hours)
- **Cohort 2**: 3 x 4.0 mg/kg (0, 24, 48 hours)

in clearing *P. falciparum* parasites in children with severe malaria.
Dose Finding Study – Study Objectives:

Secondary objectives:

y Comparison of tolerability, safety, efficacy and ease of administration of the 2 Artesunate dosing regimens

y Evaluation of differences in the pharmacokinetic profile of iv Artesunate by patient age and clinical presentation
Primary efficacy endpoint: 99% parasite clearance at 24h
Per protocol achieved in:

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<tr>
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<th>5 dose group</th>
<th>3 dose group</th>
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<tbody>
<tr>
<td>PP</td>
<td>85% (77%-93%)</td>
<td>78% (69%-87%)</td>
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100%, 99%, 90% and 50% parasite clearance in the two groups:

<table>
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<tr>
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<th>5 dose group</th>
<th>3 dose group</th>
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<tbody>
<tr>
<td>PC100 in hours</td>
<td>36 (30-48)</td>
<td>36 (30-48)</td>
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<tr>
<td>Median (25% and 75% IQ)</td>
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<tr>
<td>PC99 in hours</td>
<td>24 (18-24)</td>
<td>18 (18-30)</td>
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<tr>
<td>Median (25% and 75% IQ)</td>
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<tr>
<td>PC90 in hours</td>
<td>18 (12-18)</td>
<td>12 (12-18)</td>
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<tr>
<td>Median (25% and 75% IQ)</td>
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<tr>
<td>PC50 in hours</td>
<td>12 (6-12)</td>
<td>12 (6-12)</td>
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<tr>
<td>Median (25% and 75% IQ)</td>
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Pharmacokinetics Artesunate

Pharmacokinetics of Artesunate were dose independent.
Pharmacokinetics of DHA showed a lower clearance in 3-dose regimen.
Dose Finding Study – Outcome:

SMAC has shown a simplified once-daily iv regimen in 3 days is equivalent to the conventional 5-day iv regimen.

➢ Next Step:
    Testing of simplified regimen by the intramuscular route vs intravenous route for optimisation of Artesunate usage.
Dose Optimization Study (Phase III/IV):

Randomized, open label, three arm, follow-up trial

yUKT (Sponsor)
yEDCTP, BMBF (Funding Body)
yGuilin (Drug Donor)
yITM, Tübingen (Project Team)
ySMAC (Investigators)
- Albert Schweitzer Hospital, Lambaréné, Gabon – Saadou Issifou
- Queen Elizabeth Central Hospital, Blantyre, Malawi – Terrie Taylor
- Kumasi University of Science and Technology, Ghana – Tsiri Agbenyega
- Medical Research Council Laboratories, Banjul, The Gambia – Kalifa Bojang
- Kenya Medical Research Institute, Kilifi/Kisumu, Kenya – Charles Newton & Bernhard Ogutu
Dose Optimization Study – Further Partners:

y St. George‘s, London – Sanjeev Krishna (Scientific Advisor)
y Quintiles, Benin&Mali (CRO)
y CenTrial, Tübingen (Data Management)
y IKP, Stuttgart (Pharmacokinetics)
y Medical University Innsbruck (Oto-Acoustic Tests)
y Vienna School of Clinical Research (Capacity Building)
Dose Optimization Study – Study Objectives:

Randomization of 1044 patients at 5 study sites in Africa

Primary objectives:

Assessment of non-inferiority of iv – and im – artesunate simplified dosing regimens to the standard im treatment:

**Cohort 1**: 3 x 4.0 mg/kg iv (0, 24, 48 hours)

**Cohort 2**: 3 x 4.0 mg/kg im (0, 24, 48 hours)

**Cohort 3**: 5 x 2.4 mg/kg im (0, 12, 24, 48 and 72 hours)

in clearing *P. falciparum* parasites in children with severe malaria.
Dose Optimization Study – Study Objectives:

Secondary objectives:

- Comparison of tolerability and safety of the 3 Artesunate dosing regimens
- Evaluation of differences in the pharmacokinetic profile of parenteral Artesunate by patient age and clinical presentation (Gabon, Ghana, Kenya)

Exploratory analysis:

- Lambaréné-Organ-Dysfunction Score (LODS)
- Oto-acoustic tests (Gabon, Ghana, Kenya)
- *In vitro* drug sensitivity (Gabon)
Dose Optimization Study – Study Status:

- Ethics approval retrieved: Gabon, Ghana, Gambia and Kenya

- First Patient First Visit: 4th July 2011 (Gabon)

- Actively recruiting sites: Gabon, Ghana and Gambia
  - Kisumu/Kenya start-up in Oct 2011
  - Malawi start-up in Dec 2011

- Recruitment Status 30th Sep 2011: 55 patients
Thank You!

SMAC Artesunate Investigator Meeting in Vienna, April 2011.