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ASX Release

Malaria 2012: Saving Lives in the Asia-Pacific Conference Update

Eastland welcomes the commitment made by the Australian Government to save lives in the Asia Pacific region by pledging AU$100 million over the next four years to scale up malaria control, contain the spread of drug resistance and advance malaria research.

Eastland's CEO, Stephen Carter, was invited to attend Malaria 2012: Saving Lives in the Asia-Pacific, a conference hosted by the Australian Government where Health and Foreign Affairs Ministers, malaria experts and senior representatives from donor groups, non-government organisations and malaria-endemic governments called for a stronger response in the Asia-Pacific, emphasising the importance of political leadership and regional coordination in the fight against Malaria.

The conference delegates discussed the challenges and opportunities for the region and developed a consensus document that will be used to brief regional leaders on the impact of malaria on development and health systems in countries outside of Africa. Malaria is a potentially fatal disease which threatens over 2 billion people each year in the Asia-Pacific Region - approximately 67% of the world's total population of people at risk of malaria.

At the conference Eastland presented two Posters outlining the Results of its earlier Clinical Trials using ArTiMist™ as a treatment for severe childhood Malaria. (Attached). Eastland's CEO said; "The conference brought together representatives of many groups including the Bill and Melinda Gates Foundation, WHO, Medicines for Malaria Venture (MMV), the Clinton Foundation, Roll Back Malaria, The Global Fund as well as Health Ministers and other senior government officials from the region. It was a conference that provided the opportunity to engage with these groups at the most senior of levels and to provide a greater understanding of the work that Eastland is doing in the fight against Malaria"

Eastland is thankful to the Australian Government and AusAID for inviting it to be involved in such an important conference, and for the opportunity to present the results of its research to a group of world leaders in Malaria.

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Pharmacokinetics of Artemether Sublingual Spray

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Abstract

Background: The majority of deaths from severe malaria in childhood are caused by the delayed administration of effective antimalarial treatment.

Methods: Fifteen children with severe *falciparum* malaria, or uncomplicated f*alciparum* malaria with gastrointestinal complications received artemether sublingual spray, ArTiMist™ 3mg/kg for 6 doses (0, 8, 24, 36, 48 and 60 h). Sparse blood sampling techniques were used. Artemether and dihydroartemsenin concentrations were measured using a validated LCMS-MS assay.

Results: Artemether (ART) is rapidly absorbed following sublingual administration. The mean C_{max} of 271ng/ml and 106.5ng/ml was reached within 1.6 h and 1.75 h for artemether and DHA respectively following first administration. respectively. On day 2, the C_{max} (outlier excluded) for artemether and DHA was 158.8ng/ml and 531.56ng/ml respectively. For all patients therapeutic plasma concentrations of artemether and DHA were rapidly achieved leading to parasite clearance in all treated patients.

Conclusions: ArTiMist™ is rapidly absorbed with high plasma concentrations of artemether and DHA reached shortly after dosing. Thirteen (86.7%) of patients had negative parasite counts by the second day of treatment. With the ease of administration and rapid absorption of ArTiMist™, effective plasma concentrations may be achieved earlier than with IV administration of medication, given the difficulty of venous access, mixing medications and time of infusions.

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Background

"The majority of deaths from severe malaria in childhood are caused by the delayed administration of effective antimalarial treatment. There is a relentless deterioration in the clinical condition of a young child with malaria who fails to get effective treatment, with death ensuing in a matter of hours or days. Any successful attempt to reduce mortality from malaria will have to explore novel possibilities for minimising such delays"[1]. ArTiMist™ is a sublingual formulation of the highly active antimalarial agent, artemether. Pharmacokinetic studies have shown that ArTiMist™ has a 2.5 fold higher bioavailability than oral artemether[2]. ArTiMist™ can be administered with minimal clinical skills even in very sick or unconscious children.

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Methods

This open label randomised comparative trial was conducted in a single study centre in Rwanda. The study protocol, patient information leaflet and written informed consent form were approved by the University Teaching Hospital Kigali Research Ethics Committee. Written informed consent was obtained from patient's authorised legal representative for all study subjects. Patients were required to have severe or complicated *falciparum* malaria (according to the WHO criteria[3]), or uncomplicated f*alciparum* malaria with gastrointestinal complications that precluded oral therapy. Thirty patients were randomly assigned to ArTiMist™ 3mg/kg for six doses (0, 8, 24, 36, 48, 60h) or intravenous quinine (20mg/kg loading followed by 10mg/kg 8 hourly). For patients allocated to the ArTiMist™ treatment arm, blood samples were taken for the determination of artemether and dihydroartemsenin (DHA) concentrations. Each patients was allocated an individual sampling schedule that was randomised and based on the segments of plasma concentration time profile. A validated LCMS-MS assay was used for the determination of artemether and DHA concentrations. WinNonlin® version 5.0.1 was used to calculate the following pharmacokinetic parameters : AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, CL/F, V/F and λ_z.

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Results

Fifteen patients were randomised to ArTiMist™. One was withdrawn due to protocol violation and was replaced. There were 15 evaluable patients for the pharmacokinetic population. As the data for one patient on Day 2 appeared unusual, the calculations are presented both with and without that patient.

Following the first administration of ArTiMist™ on Day 1, the plasma concentrations of artemether rapidly increased to reach the maximum concentration (C_{max}) of 271ng/mL within 1.58 hours (T_{max}). In all patients sampled at 15 minutes after dosing, drug was detectable in the plasma with the mean concentration at 15 minutes being 57.7ng/ml. Plasma concentration had reached nearly 200ng/mL by 45 minutes after first dosing. The $t_{1/2}$ was 1.55h and $AUC_{0-\infty}$ was 788ng/mL.h. The Day 2 T_{max} and C_{max} were 2.28h and 181ng/mL respectively. The $t_{1/2}$ and $AUC_{0-\infty}$ were however higher at 4.5h and 1004ng/mL.h.

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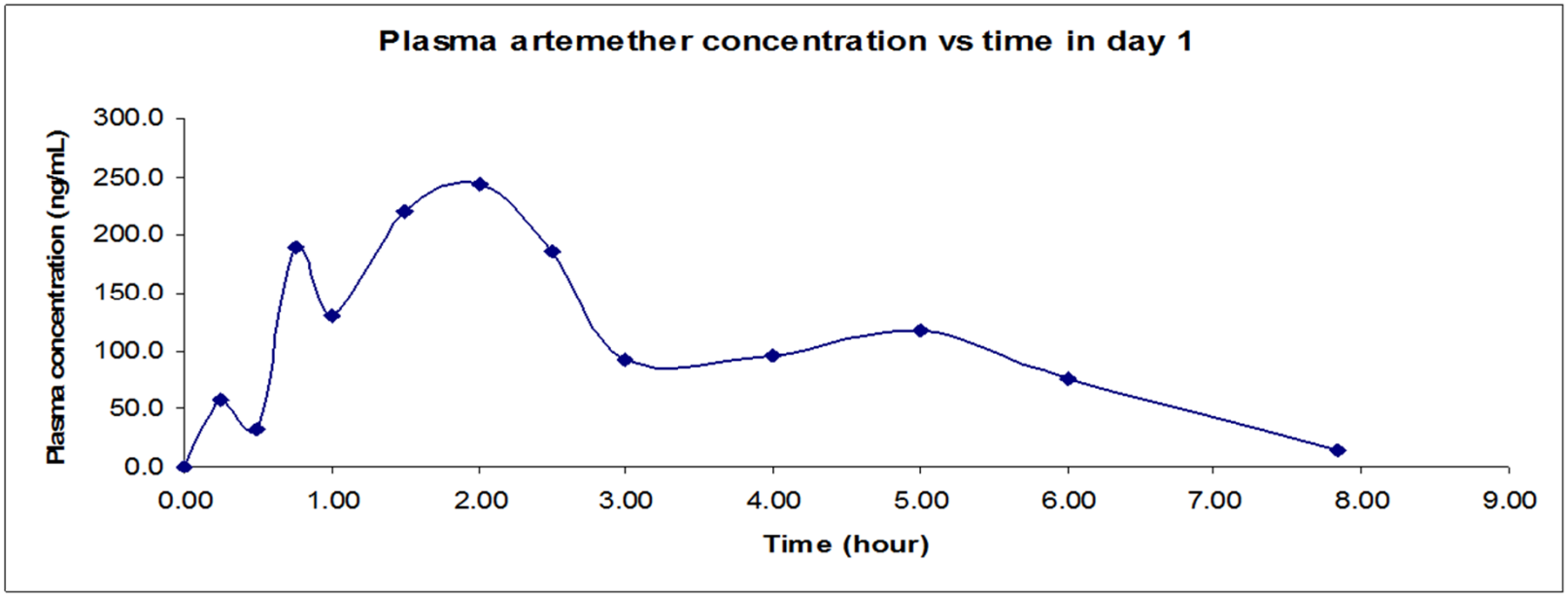
Results Day 1

Artemether Day 1	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	AUC_{inf} (ng/mL.h)	V/F (L)	CL/F (L/h)
N	11	15	15	15	11	11	11
Mean	1.55	1.58	271.2	671.8	780.33	271.99	172.1
CV%	23.7	66.1	90	91.9	101.1	152.4	201.7



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Results Day 1

Dihydroartemsenin	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	AUC_{inf} (ng/mL.h)	V/F (L)	CL/F (L/h)
N	7	15	15	15	7	7	7
Mean	1.12	1.75	106.5	255.89	432.84	330.09	313.73
CV%	35.8	52.6	139.9	152.4	139.7	79.4	117.9

Following ArTiMist™ administration on Day 1, artemether is rapidly converted to (DHA) dihydroartemsenin. DHA is detectable within about 45 minutes and reached a maximal concentration (C_{max}) of 107ng/mL after 2 hours (T_{max}). The $t_{1/2}$ and $AUC_{0-\infty}$ were 1.12h and 432 ng/mL.h respectively.

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Results Day 2

Artemether Day 2	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	AUC_{inf} (ng/mL.h)	V/F (L)	CL/F (L/h)
N	8	11	11	11	8	8	8
Mean	4.53	2.28	181.5	716.96	1004.75	480.72	80.7
CV%	107.2	89.7	59	63.1	118.1	145.1	86.6
Mean (Excluding Outlier)	2.94	2.36	158.8	619.83	601.49	531.69	90.72
CV% (Excluding Outlier)	66.9	90.7	50.6	54.0	58.8	138.7	74.3

The Day 2 T_{max} and C_{max} were 2.28h and 181ng/mL respectively. The $t_{1/2}$ and $AUC_{0-\infty}$ were however higher at 4.5h and 1004ng/mL.h.

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Results Day 2

Dihydroartemsenin Day 2	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)	AUC_{inf} (ng/mL.h)	V/F (L)	CL/F (L/h)
N	8	11	11	11	8	8	8
Mean	3.10	2.71	572.96	2282.99	4418.82	361.41	113.93
CV%	157.2	85.1	63.2	107.0	180.3	255.0	238.3
Mean (Excluding Outlier)	1.38	2.58	531.46	1604.38	1620.90	410.32	130.08
CV% (Excluding Outlier)	33.2	92.6	66.4	62.5	61.3	240	222

On Day 2, the parameters (excluding outlier) were: C_{max} 531.5ng/ml and $AUC_{0-\infty}$ was 1621 ng/mL.h.

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Results

Summary of drug concentration and relationship to response

Patient	Artemether		DHA		Parasite clearance[a]
	C_{max} (ng/ml)	T_{max} (Day/hour)	C_{max} (ng/ml)	T_{max} (Day/hour)	
001-003	116.3	Day 1; 1.66h	31.0	Day 1;2h	Day 2 predose
001-004	101.5	Day 1; 3h	47.3	Day 1; 3h	Day 1 18 h
001-005	295.6	Day 1; 0.75h	22.2	Day 1; 0.75h	Day 3 12 h
001-007	285.6	Day 1; 0.75h	530.4	Day 2; 1.5h	Day 7
001-012	263.6	Day 2; 0.75h	432.0	Day 2; 2h	Day 2 predose
001-013	64.6	Day 1; 0.5h	8.5	Day 1; 1h	Day 2 predose
001-015	243.6	Day 2; 7.83h	788.8	Day 2; 7.83h	Day 2 6 h
001-018	179.3	Day 1; 2.5h	165.3	Day 1; 2h	Day 1 18 h
001-020	160.4	Day 1; 1h	81.7	Day 1; 1.5h	Day 1 12 h
001-022	919.2	Day 1; 2h	1215.2	Day 2; 1.5h	Day 1 18 h
001-023	368.8	Day 1; 2h	764.8	Day 2; 1h	Day 2 12 h
001-025	189.7	Day 2; 3h	478.4	Day 2; 2h	Day 2 predose
001-026	180.0	Day 1; 1h	684.4	Day 2; 0.75h	Day 2 predose
001-029	528.0	Day 1; 2.5h	280.0	Day 2; 2.5h	Day 1 18 h
001-111	597.6	Day 1; 1h	988.0	Day 2; 4h	Day 2 predose

[a] Time of first negative parasite smear

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Discussion

Minimising any delay in administering adequate plasma concentrations of effective antimalarial treatment remains a key challenge in the management of malaria. Sublingual administration of artemether (ArTiMist™) is easy to administer and does not require any significant degree of clinical skill. No additional medical equipment is required for administration and no preparation nor clinical supervision is required for the duration of dosing. The risks associated with parenteral administration are avoided, even in very sick or unconscious patients. It is rapidly absorbed with plasma concentrations approximating 200ng/ml within 45 minutes of administration. It is rapidly converted to the more active metabolite DHA. Within 24 hours of the first administration, eleven of the fifteen patients (73.3%) had their first negative parasite smear. Sublingual administration of artemether has the potential to reduce deaths from severe malaria by reducing the delay in the administration of effective antimalarial treatment.

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Conclusions

1. ArTiMist™ is rapidly absorbed with high plasma concentrations of artemether and DHA reached shortly after dosing
2. Thirteen (86.7%) of patients had negative parasite counts by the second day of treatment
3. With the ease of administration and rapid absorption of ArTiMist™, effective concentrations may be achieved earlier than with IV administration of medication, given the difficulty of venous access, mixing medications and time of infusions

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Next Stage
Phase III

- Eastland have recently completed a Phase III, randomized, open labelled, active controlled, multi-centre, superiority trial of ArTiMist™ versus intravenous quinine in 150 children with severe or complicated *falciparum* malaria, or uncomplicated *falciparum* malaria with gastrointestinal complications.
- The study was carried out over 3 sites in Sub Saharan Africa Ghana, Burkina Faso and Rwanda.
- Initial results appear to confirm earlier studies.
- Final report due January 2013.

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Next Phase
Pre-Referral

Eastland are currently in the planning stage of a early intervention study titled:

- Open label randomised comparative study of the efficacy, tolerability and pharmacokinetics of ArTiMist™ an artemether sublingual spray, intramuscular artemether or artesunate suppositories in Papua New Guinean children with severe malaria or who are unable to swallow oral antimalarial therapy
- The study will compare the ease of use and patient acceptability as well as the standard medical endpoints

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References

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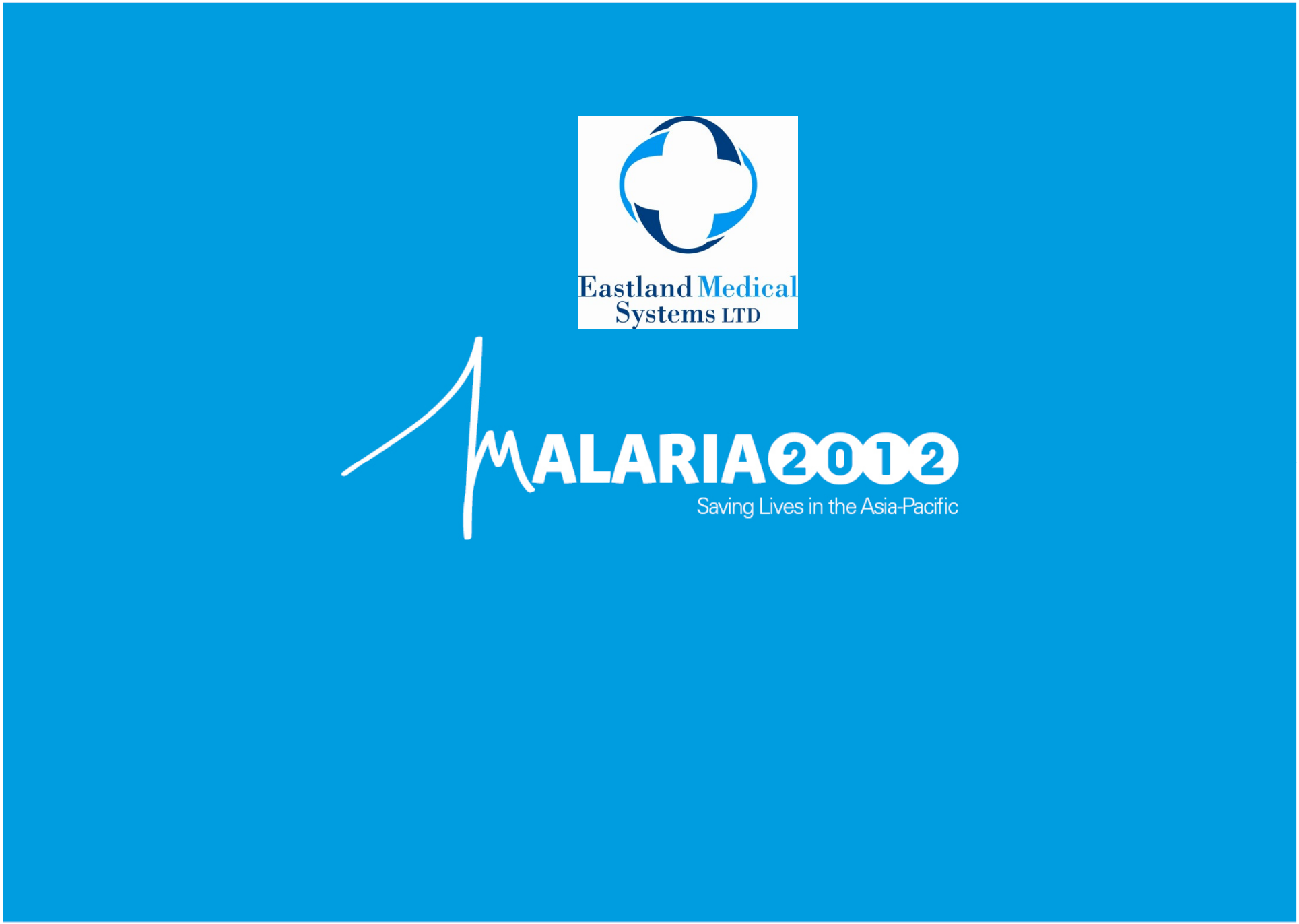

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ArTiMist™

Sublingual Artemether in Severe Childhood Malaria.

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Abstract

BACKGROUND:
The majority of deaths from severe malaria in childhood are caused by the delayed administration of effective antimalarial treatment.
METHODS:
30 children with severe *falciparum* malaria, or uncomplicated malaria with gastrointestinal complications were randomised to receive artemether sublingual spray, ArTiMist 3mg/kg for 6 doses or intravenous quinine 20mg/kg loading then 10mg/kg tds.
RESULTS:
For the primary efficacy parameter of parasitological success, 14 (93%) of ArTiMist™ treated patients and 10 (66.7%) of quinine treated patients had parasitological success. Patients allocated to ArTiMist™ had similar times for the PCT_{90} and PCT_{50}, the additional primary efficacy parameters. For the parasitological related secondary efficacy parameters of PRR_{12}, PRR_{24} and PCT's, these were similar for both treatment groups. There were no clinical or statistical (where tested) differences between the treatments. For the clinically related secondary efficacy parameters, time to normal per os status, fever clearance time (FCT), early treatment failures and number of new infections or recrudescence's, patients responded in a similar way to both treatments.
CONCLUSIONS:
1) 14 (93.3%) of patients met the primary endpoint criteria compared to 10 (66.7%) of patients treated with intravenous quinine.
2) For all other primary and secondary efficacy parameters, there was no statistically or clinically significant difference between treatments.
3) both treatments were safe and well tolerated and
4) ArTiMist™ has good local tolerability.

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Background

The majority of deaths from severe malaria in childhood are caused by the delayed administration of effective antimalarial treatment. There is a relentless deterioration in the clinical condition of a young child with malaria who fails to get effective treatment, with death ensuing in a matter of hours or days. Any successful attempt to reduce mortality from malaria will have to explore novel possibilities for minimising such delays"[1]. ArTiMist™ is a sublingual formulation of the highly active antimalarial agent, artemether. Pharmacokinetic studies have shown that ArTiMist™ has a 2.5 fold higher bioavailability than oral artemether[2]. ArTiMist™ can be administered with minimal clinical skills even in very sick or unconscious children.

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Methods

This open label randomised comparative trial was conducted in a single study centre in Rwanda between November 2009 and January 2010. The study protocol, patient information leaflet and written informed consent form was approved by the University Teaching Hospital Kigali Research Ethics Committee. Written informed consent was obtained from patients authorised legal representative for all study subjects. Patients were required to have severe or complicated falciparum malaria (according to the WHO criteria[3]), or uncomplicated falciparum malaria with gastrointestinal complications that precluded oral therapy. Thirty patients were randomly assigned to ArTiMist™ 3mg/kg for six doses or intravenous quinine (20mg/kg loading followed by 10mg/kg 8 hourly). Patients were monitored regularly for parasite counts (by blinded readers), clinical status and safety and were followed up for 28 days. The main primary study endpoint was parasitological success defined a s a reduction in parasite count of ≥ 90%. Additional primary endpoints were, time for parasites count to fall 90% (PCT_{90}) and 50% (PCT_{50}). Secondary endpoints are defined in Table 2 The data was managed on Clindex® version 3.9.701 and SAS® for windows version 9.0 was used for statistical analysis. For parasitological success, Fishers exact test was used to compare the difference and life table curves were constructed for PCT_{90} and PCT_{50} and compared with log rank test.

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Results

Thirty one patients were randomised to treatment (16 ArTiMist™, 15 quinine). One patient randomised to ArTiMist™ was withdrawn due to protocol violation and was replaced. All other patients completed the study as per protocol.

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Results

Demographics and Baseline Characteristics

Parameter		ArTiMist™	Quinine
Age (years)	Mean (SD) Range	3.03 (1.5) 0.6 – 5.5	3.64 (2.5) 0.2-7.5
Gender	Female Male	9 7	7 8
Weight (kgs)	Mean (SD) Range	11.16 (2.541) 7.0 – 15.0	11.35 (3.342) 5.0 – 15.0
Baseline Parasite count (parasite per mcl)	Median Range	19660 1480 - 712307	21800 1120 - 109440
Disease definition Severe or complicated Uncomplicated	 Number (%) Number (%)	 10 (62.5%) 6 (37.5 %)	 12 (80.0%) 3 (20.0%)
Number of patients with pre existing condition	Number (%)	12 (75.0%)	14 (93.3)
Ability to eat/drink normally for age (baseline)	Yes (Number (%)) No (Number (%))	0 (0%) 16 (100%)	0 (0 %) 15 (100%)
Baseline BCS	5 Number (%)) <5 (Number (%))	13 (81.3%) 3 (18.7%)	12 (80.0%) 3 (20.0%)
Baseline Pulse rate (bpm)	Mean (SD) Range	142.38 (24.674) 114 - 194	144.27 (15.135) 118 - 171
Baseline temperature °C	Mean (SD) Range	38.17 (1.279) 35.6 – 40.8	37.81 (0.809) 36.2 – 39.2

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Results

Primary and Secondary Endpoints

	ArTiMist™	Quinine	P value	Confidence Intervals
Parasitological Success				
Yes (N (%))	14 (93.3%)	10 (66.7%)	0.17	-0.3% - 53.7%
No (N (%))	1 (6.7%)	5 (33.3%)		
PCT (90) (mean(SD)) Hours	17.6 (7.34)	19.8 (13.59)	0.70	0.48 – 3.01
PCT (50) (mean(SD)) Hours	12.0 (6.48)	10.8 (7.42)	0.76	0.34 – 2.18
PRR (12) (median(range)) %	79.6 (-220 - 100)	75.9 (-58 – 100)	N/A	-66.0 – 39.1
PRR (24) (median(range) %	100.0 (77 - 100)	96.9 (53 – 100))	N/A	-0.4 - 17.7
PCT (mean(SD)) Hours	35.7 (41.97)	51.2 (79.04)	N/A	N/A
Time to normal per os (mean (SD)) Hours	17.7 (11.31)	20.7 (9.44)	N/A	N/A
FCT (mean (SD)) hours	89.9 (72.8)	86.1 (25.8)	N/A	N/A
Number of **early treatment failures** (N (%))	0 (0.0%)	0 (0.0%)	N/A	N/A
Number of recrudescence or new infections (N (%))	3 (18.8%)	4 (26.7%)	N/A	-37.4 – 21.5

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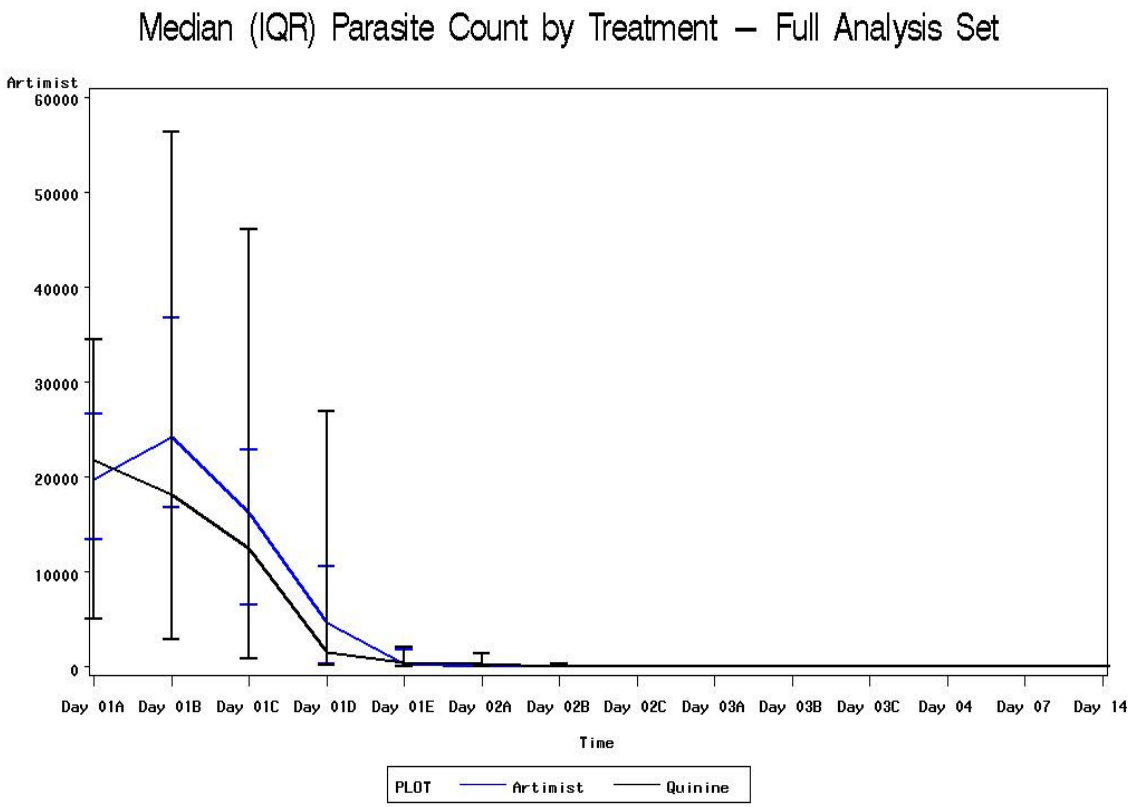
Results

Parasite Count by Treatment- Full Analysis Set



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Discussion

In this small exploratory study comparing ArTiMist™ with intravenous quinine, there were no clinically or statistically significant differences between the two treatments. Sublingual administration of artemether lead to rapid clearance of parasites and recovery of clinical status. Both treatments were safe and well tolerated and the investigator did not attribute any adverse events to either treatment. The local tolerability of ArTiMist™ was good. ArTiMist™ is easy to administer and does not require any significant degree of clinical skill. No additional medical equipment is required for administration and no preparation nor clinical supervision is required for the duration of dosing. The risks associated with parenteral administration are avoided, even in very sick or unconscious patients. Sublingual administration of artemether has the potential to reduce deaths from severe malaria by reducing the delay in the administration of effective antimalarial treatment.

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Conclusion

1. ArTiMist™ has good local tolerability in children
2. 14 (93.3%) of ArTiMist™ treated patients met the primary endpoint criteria (reduction in parasite count of ≥ 90% of baseline at 24 hours after the first dose) compared to 10 (66.7%) of patients treated with intravenous quinine
3. For all other primary and secondary efficacy parameters, there was no statistically or clinically significant difference in the way patients responded to ArTiMist™ or quinine.
4. Both treatments were safe and well tolerated

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Next Stage
Phase III

- Eastland have recently completed a Phase III, randomized, open labelled, active controlled, multi-centre, superiority trial of ArTiMist™ versus intravenous quinine in 150 children with severe or complicated *falciparum* malaria, or uncomplicated *falciparum* malaria with gastrointestinal complications.
- The study was carried out over 3 sites in Sub Saharan Africa Ghana, Burkina Faso and Rwanda.
- Initial results appear to confirm earlier studies.
- Final report due January 2013.

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Next Phase
Pre-Referral

Eastland are currently in the planning stage of a early intervention study titled:

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- The study will compare the ease of use and patient acceptability as well as the standard medical endpoints

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References and Glossary

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1. WHO. Roll Back Malaria Partnership: Malaria and Children. [Online] 2008. [Cited: 07 September 2009.] http://www.rbm.who.int/cmc_upload/0/000/015/367/RBMInfosheet_. Journal Article,
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3. WHO. *Guidelines for the treatment of malaria.* World Health Organisation. Geneva : WHO/HTM/MAL/2006-1108, 2006.

Secondary endpoints Glossary of Terms:

- $PRR_{(12)}$ and $PRR_{(24)}$ = parasite reduction ratio after 12h and 24h (% reduction in parasitemia from baseline)
- PCT = parasite clearance time (time until the first of two successive parasite negative smears
- Time to normal per os = time for patients to return to normal per os for at least 6 hours
- FCT = fever clearance time (disappearance of fever for at least 24 h)
- Early treatment failure = D2 parasitemia > Day 0; or parasitemia and fever on Day 3; parasitemia Day 3 ≥ 25% of Day 0 parasitemia
- Recrudescence or new infection = failure to have full parasite eradication at Day 10, 14, 21 or 28

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