ASX Release

CLINICAL TRIAL RESULTS PRESENTED AT ICAAC IN BOSTON, USA

Eastland Medical Systems Ltd (ASX:EMS) is delighted to announce that the results of the recently completed Rwandan clinical trial have been presented to the international scientific community in Boston at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) conference. The presentations received an exceptional amount of interest from the pharmaceutical, academic and investment communities.

The presentations clearly highlight the speed of ArTiMist™ absorbtion from the easily accessible sublingual route and emphasise the clinical response rate of patients administered ArTiMist™ when compared to the WHO Recommended standard of care, intravenous quinine.

Dr Stephen Rulisa, the study principal investigator states that "the drug ArTiMist™ is highly acceptable to patients/carers and staff, especially due to the ease of administration. It is capable of delivering a highly effective anti-malarial treatment that does not require additional expertise such as setting up IV lines and preparing medications, resulting in the most rapid possible administration."

Moving forward, Eastland will be pursuing two major paths to build value for its shareholders. On the one hand, Eastland will progress the initial opportunities identified by Sydney based AFG Venture Group that have arisen from the positive results for ArTiMist™ obtained to date. In parallel, the clinical dossier will be further strengthened via data obtained from the upcoming multi country confirmatory trial which has just received Ethics approval and is due to start on schedule.

Recent research has shown that there is a very significant uplift in the commercial value of therapeutic products as the clinical dossier is expanded and strengthened.

Copies of the two ICAAC presentations are attached.

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Highlights

- **Positive results achieved from Phase I multi and single dose clinical studies for ArTiMist™ indicating the formulation was well tolerated and showed no adverse effects in any of the study subjects.**
- **ArTiMist™ Clinical Field Trial completed in February 2010 in Rwanda.**
- **Very Positive successful results achieved from Phase IIa ArTiMist ™ trial.**

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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 falciparum 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 dihydroartemesin 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 absorbtion 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

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.

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 (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 dihydroartemesin (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.

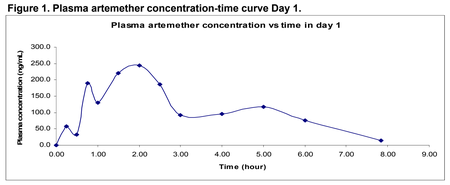
Results

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.

Table 1. Summary of pharmacokinetic parameters

	$t_{1/2}$ (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)
Artemether Day 1							
N	11	15	15	15	11	11	11
Mean	1.55	1.58	271.2	671.08	780.33	271.99	172.10
CV%	23.7	66.1	90.0	91.9	101.1	152.4	201.7
Artemether Day 2							
N	8	11	11	11	8	8	8
Mean	4.53	2.28	181.5	716.96	1004.75	480.72	80.07
CV%	107.2	89.7	59.0	63.1	118.1	145.1	86.6
Mean (excel outlier)	2.94	2.36	158.8	619.83	601.49	531.69	90.72
CV(%) (Excel outlier)	66.9	90.7	50.6	54.0	58.8	138.7	74.3
DHA Day 1							
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
DHA Day 2							
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 (excl outlier)	1.38	2.58	531.46	1604.38	1620.90	410.32	130.08
CV% (excl outlier)	33.2	92.6	66.4	62.5	61.3	240	222

Figure 1. Plasma artemether concentration-time curve Day 1.



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 four 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.

Following ArTiMist™ administration on Day 1, artemether is rapidly converted to (DHA) dihydroartemesinin. 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. On Day 2, the parameters (excluding outlier) were: C_{max} 531.5ng/ml and $AUC_{0-\infty}$ was 1621 ng/mL.h.

Sublingual administration of artemether does not appear to affect the conversion to DHA. The ratios of DHA:ART are 0.39 and 3.34 for the C_{max} on Days 1 and 2 respectively and 0.55 and 2.69 for AUC on Days 1 and 2 respectively. The metabolic ratios, together with the apparent clearance (CL/F) and apparent volume of distribution (V/F) appear to be within the ranges reported in the literature [4-8].

Table 2. 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

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.

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 absorbtion 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

References

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Sublingual Artemether in Severe Childhood Malaria

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Abstract (revised)

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.

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.

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.

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.

Table 1. 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

Figure 1: Median (IQR) Parasite Count by Treatment — Full Analysis Set

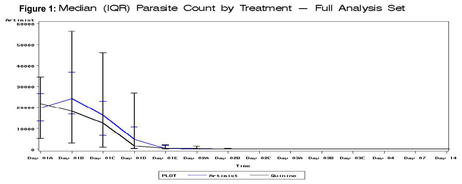

Table 2. Primary and secondary endpoints

	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

Secondary endpoints:
•$PRR_{(12)}$ and $PRR_{(24)}$ = parasite reduction ratio after 12h and 24h (% reduction in parasitaemia 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 parasitaemia > Day 0; or parasitaemia and fever on Day 3; parasitaemia Day 3 ≥ 25% of Day 0 parasitaemia
•Recrudescence or new infection = failure to have full parasite eradication at Day 10, 14, 21 or 28

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. A number of highly effective antimalarials are currently available. Sublingual administration of artemether has the potential to reduce deaths from severe malaria by reducing the delay in the administration of effective antimalarial treatment.

Conclusions

1. **ArTiMist™ has good local tolerability in children**
2. **14 (93.3%) of 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**

References

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