Subject: FW: Paediatric artemether lumefantrin

From: Herwig Jansen [mailto:herwig.jansen@dafra.be]
Sent: 14 February 2007 11:35
To: Hill, Suzanne
Subject: Paediatric artemether lumefantrin

Stability of the Artemether/lumefantrine suspension:

The bottles containing Artemether/lumefantrine powder for suspension were opened and water was added. After closing the mixture is shaken and a suspension is formed. The volume is adjusted by adding more water and again the bottle is shaken. This uspension (in which the water insoluble lumefantrine and Artemether or freely floating) is then kept at 30°C in a hulidity room of 65%. Samples are taken at time zero and then at time points 14 days and 30 days. Artemether and lumefatnrine are assayed by hplc. Results are expressed in percentage compared to the value at time zero. The product is perfectly stable for the time period considered.

1.1. After reconstitution and/or first opening of the product

Co-Artesiane powder for suspension is suspended with water and kept at 30°C during 30 days.
Results below at time T=0, T= 14 days and T= 30 days

Batch Co-Artesiane	% Artemether	% Lumefantrine
T0	100	100
T14	96	96
T30	92	97

As can be seen the assay gives adequate results (concentrations of the active pharmaceutical ingredient should be above the 90 % level). Even during storage at 30°C the made up suspension is keeping its full quality over a period of 30 days.

Bioequivalence studies of Artemether lumefantrine paediatric suspension in comparison with Co-artem (Novartis) tablets.

2007/97 - BBRC/EX/06/021: A relative bioavailability study for Fixed Dose Combination (FDC) comparing Coartem® Tablets (containing Artemether 20 mg and Lumefantrine 120 mg) of Novartis Pharmaceuticals Limited, EU with Co-artesiane® dry powder for suspension (containing β-Artemether 360 mg and Lumefantrine 2160 mg in 45.6 g dry powder for suspension of 120 ml) of Dafra Pharma NV, Belgium in 42 + 6 healthy adult human subjects.

→ ***Analytical stability testing until 60 days is over. Period I started on 4 February 2007. It is expected that period II will start on 25 February 2007. The analysisperiod is from 7 to 21 March 2007. The report will be available on 28 March 2007***

COUNTRY AND STUDY SITE

India, Bombay Bioresearch Centre (CRO)

INVESTIGATORS

Dharmendra Ved	(Clinical, Statistical and Pharmacokinetic Facility)
Dr. Shrikant Rane	(Bioanalytical Facility)
Dr. Prashant Kulkarni	(Principal Investigator)
Eddie Palia	(Pathological Testing Facility)
Dr. Avinash Phadke	(Pathological Testing Facility)

OBJECTIVES

Pharmacokinetics: To compare the rate and extent of absorption of Artemether and Lumefantrine after administration of Fixed Dose Combination (FDC) comparing Coartem® Tablets (containing Artemether 20 mg and Lumefantrine 120 mg) of Novartis Pharmaceuticals Limited, EU with Co-artesiane® dry powder for suspension (containing β-Artemether 360 mg and Lumefantrine 2160 mg in 45.6 g dry powder for suspension of 120 ml) of Dafra Pharma NV, Belgium under fed condition in healthy adult human subjects in a randomised crossover study.

Safety: To monitor the safety and tolerability of a single dose of Co-artesiane® dry powder for suspension (containing β-Artemether 360 mg and Lumefantrine 2160 mg in 45.6 g dry powder for suspension of 120 ml) of Dafra Pharma NV, Belgium, when administered in healthy human subjects.

SAMPLE SIZE

Total 42 plus up to 6 reserve healthy subjects who meet all inclusion and none of the exclusion criteria have been recruited.

Clinical ongoing studies with the Artemether/lumefantrine suspension for paediatric use.

In agreement with local authorities in African countries Dafra has accepted to do the following studies:

1. 2007/93: **A randomized open-label trial of the efficacy of artemether/ lumefantrine suspension compared with artemether/lumefantrine tablets for the treatment of uncomplicated *plasmodium falciparum* malaria in children less than five years in Western Kenya**

COUNTRY AND STUDY SITE

Kenya, Ahero Health Centre in Nyando District 22km from Kisumu town

INVESTIGATORS

Dr. Elizabeth A. Juma	(Kenya Medical Research Institute)
Dr. Charles Obonyo	(Kenya Medical Research Institute)
Dr. Willis Akhwale	(Ministry of Health, Division of Malaria Control)
Dr. Bernhards Ogutu	(Kenya Medical Research Institute)

OBJECTIVES

Primary objective: The primary objective of the study is to compare PCR corrected cure-rates on day 14 and 28 in children aged 6 - 59 months with uncomplicated malaria, treated with either conventional AL (Coartem®) or AL suspension (Co-artesiane®) in Western Kenya

Specific objectives:

1. Determination of Adequate Clinical and Parasitological Response (ACPR) at days 14 and 28 for 6-dose 3-day regimen of AL tablets and 3 dose/ 3 day AL suspension
2. To determine and compare proportion of children with gametocytes on days 0, 7, 14, and 28
3. Monitor any possible adverse reactions following use of both drugs

SAMPLE SIZE

The sample size for each arm is 127 patients

2. An open randomized clinical trial comparing two different oral formulations of artemether/lumefantrine (fixed dose over 3 days) on Plasmodium falciparum malaria in Rwandese children.

COUNTRY AND STUDY SITE

Rwanda,

NVESTIGATORS

PNLP Rwanda

OBJECTIVES

Main objective: To test the hypothesis that an AL suspension (Co-artesiane®) is not inferior in efficacy to the same drug administered as a tablet (Coartem®), measured by the primary endpoint: PCR corrected Adequate Clinical and Parasitological Response (ACPR) on day 28.

Secondary objectives:

1. To compare factors, known to influence patient compliance, between treatment arms. Information on side effects (clinical and biological tolerance) and patient's appreciation of the therapy will be obtained by means of a questionnaire
2. To identify the type and/or reason for treatment failure of each specific patient.
3. To compare types of treatment failure between the three treatment groups, categorized into three subgroups: early treatment failure (ETF), late parasitological failure (LPF), late clinical failure (LCF).
4. To assess and compare parasite clearance between treatment arms.
5. To assess and compare fever clearance between treatment arms.
6. To assess and compare re-infection between treatment arms.
7. To determine and compare the gametocyte carriage index between treatment arms.

SAMPLE SIZE

The sample size for each arm is 100 patients